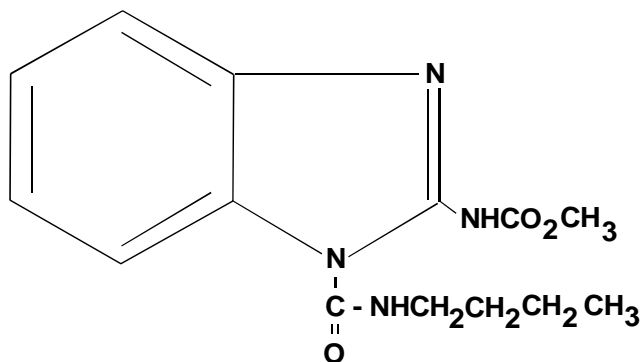


BENOMYL

RISK CHARACTERIZATION DOCUMENT



 California Environmental Protection Agency
Department of Pesticide Regulation

October 1999

RCD 99-01

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION**

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(Benlate®)

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Medical Toxicology, and Worker Health and Safety Branches

Department of Pesticide Regulation

California Environmental Protection Agency

June 30, 1999

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DPR acknowledges the review of this document by the
Office of Environmental Health Hazard Assessment

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SUMMARY

Benomyl (methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate; CAS #17804-35-2) is a systemic fungicide used to control a wide range of fungal diseases of fruits, nuts, vegetables, field crops, turf, and ornamentals. Benomyl entered the risk assessment process because of teratogenicity, oncogenicity, reproductive toxicity, and adverse effects on the liver caused by chronic exposure.

Environmental Fate- Photolysis is not a significant contributor to the degradation of benomyl. Under light or dark conditions, the half-life of benomyl in buffered (pH 5) solutions was 3-4 hours. In the field, the half-life of benomyl was 3 days. The principal degradation products of benomyl were methyl 2-benzimidazolecarbamate (MBC) and a volatile compound, *n*-butyl isocyanate. In water, *n*-butyl isocyanate rapidly hydrolysed to butylamine and carbon dioxide, with a half-life of 13.8 minutes. The half-life of MBC under aerobic conditions in non-sterile soil was 320 days. Under anaerobic conditions, the half-life of MBC was 743 days. Under field conditions, the half-life of MBC ranged from 51 to 83 days, depending upon soil type and weather conditions. Because of low water solubility and immobility in soil, benomyl and MBC are unlikely to become groundwater contaminants.

Pharmacokinetics- Benomyl was rapidly metabolized in mammals via hydroxylation and ester hydrolysis in the liver to 2-benzimidazolecarbamic acid methyl ester (MBC) and to methyl 5-hydroxy-2-benzimidazolecarbamate (5-HBC). Neither benomyl, nor MBC accumulated in any body tissues. Approximately 85% of an oral dose of radiolabeled benomyl was excreted in the urine of a rat. As these data were derived from a single animal, the 85% absorption of benomyl was not considered significantly different from 100% oral absorption. Likewise, the oral absorption of MBC, calculated as 85% from urinary data in a small number of animals, was considered to be not different from 100%. Approximately 56% of an oral dose was excreted in the urine of mice, rabbits and sheep. Elimination of MBC and benomyl was primarily via the urine, and was 95% complete 96 hours after oral administration, or 24 hr. after intravenous administration. The amount of benomyl absorbed dermally by rats ranged from 0.03% to 3.5%, depending upon the duration and the amount applied to the skin. Approximately 95% of the dermally absorbed dose was excreted in the urine, with 4% excreted in the feces. None of the submitted or published studies addressed the metabolic fate of *n*-butyl isocyanate in mammals.

Acute Toxicity- The oral LD₅₀ for benomyl and MBC in both male and female rats was greater than 10,000 mg/kg. The dermal median lethal dose of benomyl for rabbits was greater than 10,000 mg/kg, and the 4-hour median lethal atmospheric concentration of benomyl was greater than 2 g/l. Benomyl caused a Category III reaction in the primary eye irritation test.

Subchronic Toxicity- In subchronic studies, the principal toxic effects of benomyl or MBC were on the germinal epithelium of the testes, and the liver. In a 70-day subchronic study, the NOEL for a single oral dose of benomyl causing sloughing of portions of the germinal epithelium in seminiferous tubules of male rats was 25 mg benomyl/kg. Rat seminiferous tubular atrophy and efferent ductal occlusions persisted at least 70 days after a single oral dose of 100 mg benomyl/kg, or greater. The 85-day NOEL for fertility in rats was 100 mg benomyl/kg-day. The 7-day lowest observed effect level (LOEL) for hepatic toxicity (portal congestion) in rats was 40 mg benomyl/kg-day.

Chronic Toxicity/Oncogenicity- Neither benomyl, nor MBC were oncogenic in rats, but both compounds caused hepatocellular adenomas and carcinomas in several strains of mice. The principal non-oncogenic effect of chronic exposure to benomyl or MBC was hepatotoxicity. In one dog study, the 2-year NOEL for hepatotoxicity (histopathological and clinical chemistry changes) in the female dog was 2.6 mg MBC/kg-day. In the study in which dogs were dosed with benomyl for two years, the NOEL for changes in clinical chemistry indicating hepatotoxicity was 15 mg/kg-day. The 2-year NOEL for hepatotoxicity (pericholangitis/ cholangiohepatitis) in the rat was 4.9 mg MBC/kg-day. The NOEL for hepatotoxicity (centrilobular hypertrophy, single cell necrosis with reparative mitotic activity, increased pigment storage in Kupffer cells, occasional scar formation, and increased liver weights) in the mouse was 23 mg MBC/kg-day. The NOEL for testicular germ cell atrophy and sperm stasis in the mouse was 75 mg MBC/kg-day.

Genotoxicity- Benomyl was not mutagenic in *Salmonella* sp. in three studies, with or without metabolic activation. MBC was positive in two of five studies in bacteria, and in one of three studies using mammalian cells. 5-Hydroxy MBC was negative in one bacterial gene mutation study. Benomyl caused chromosomal aberrations at 1000 mg/kg in mice, and sister chromatic exchanges in CHO cells. MBC was reported to cause spindle effects in HeLa cells. Neither benomyl nor MBC caused an increase in DNA repair in primary mouse or rat hepatocytes. MBC did not produce differential growth inhibition or cytotoxicity in *B. subtilis*.

Taken together, these results suggest that MBC (or an impurity which is not always present) possesses some genotoxic activity.

Reproductive Toxicity- No specific reproductive effects of benomyl were observed in female rats; however, male testicular function was adversely affected. The parental female NOEL was 234 mg benomyl/kg-day, based on a decrement in body weight gain. The NOEL for decreased testicular sperm counts, decreased testicular weight, and degeneration and atrophy of seminiferous tubules was 28.2 mg benomyl/kg-day. The pup NOEL was 28.2 mg benomyl/kg-day based on lower birth weight and decrement in body weight gain. Acute exposure to MBC on the afternoon of proestrus caused aneuploidy in hamster oocytes leading to early pregnancy loss.

Developmental Toxicity- Benomyl and/or MBC were teratogenic in rats, rabbits, and mice. In the absence of maternal toxicity, benomyl caused enlarged lateral ventricles, enlarged renal pelves, delayed ossification, hydrocephaly, microphthalmia and anophthalmia, fused ribs, fused vertebrae, and decreased ossification in the tail in rats with a NOEL of 30 mg/kg-day. In rabbits, the NOEL for maternal toxicity (weight loss) and terata (fused and/or split ribs and asymmetric vertebrae) was 20 mg MBC/kg-day. The rabbit NOEL for developmental toxicity (post-implantation loss) was 10 mg MBC/kg-day. In mice, the NOEL for developmental effects (increased incidence of supernumerary ribs, enlarged renal pelves, cleft palate, hydronephrosis, fused ribs, fused vertebrae, short and/or kinky tail, and delayed ossification in vertebral centra) was 50 mg benomyl/kg-day.

Neurotoxicity- Neither benomyl nor its metabolite, MBC, caused any histopathological changes indicative of delayed neurotoxicity in the chicken. The NOEL for clinical signs (ataxia, low carriage, wing droop) in the chicken was 2,500 mg benomyl/kg. The NOEL for clinical signs (liquid stools, urine-stained fur) in the rat was 500 mg benomyl/kg. There was no indication, behaviorally or histopathologically, of delayed neurotoxicity in the rat.

Hazard Identification- The principal toxicological effects of benomyl are teratogenicity, oncogenicity, reproductive toxicity, and adverse effects on the liver caused by repetitive dosing. A no-observed-effect level (NOEL) of 15 mg benomyl equivalents/kg for post-implantation loss in rabbits was used as the basis for estimating acute margins of exposure from potential exposures to benomyl. Margins of exposure for potential annual exposure to benomyl were calculated using a 1-year critical NOEL of 15 mg benomyl/kg-day for hepatotoxicity (histopathological changes in the liver and elevated serum alkaline phosphatase) in dogs. The excess lifetime risk of cancer from potential exposure to benomyl was assessed using a maximum likelihood estimate (MLE) for human cancer potency of $2.8 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$, with an upper bound (95% confidence level) of $4.3 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$ based on hepatoblastomas in female mice.

Dietary Exposure- Potential acute (daily) ingestion of benomyl for all labeled uses, based on the 95th percentile of user-day exposure for all population subgroups, ranged from 11 to 39 $\mu\text{g/kg-day}$. Nursing infants, less than 1 year of age had the highest potential daily dietary exposure to benomyl when all food uses were considered. The mean potential chronic (annual) dietary exposure for all population subgroups ranged from 0.7 to 3.2 $\mu\text{g/kg-day}$. Children, 1 to 6 years of age, had the highest potential exposures.

Occupational Exposure- Average potential daily occupational exposures to benomyl ranged from 1.3 $\mu\text{g/kg-day}$ for ground applicators working with strawberries to 66.5 $\mu\text{g/kg-day}$ for mixer/loaders associated with aerial applications on almonds. Potential annual occupational exposures to benomyl ranged from 0.05 $\mu\text{g/kg-day}$ for airblast applicators working with stone fruit to 3 $\mu\text{g/kg-day}$ for field workers associated with wine grapes. Lifetime average daily dosages ranged from 0.03 $\mu\text{g/kg-day}$ for airblast applicators working with stone fruit to 1.6 $\mu\text{g/kg-day}$ for field workers associated with wine grapes.

Combined daily dietary and potential average daily occupational exposures to benomyl ranged from 13 $\mu\text{g/kg-day}$ for ground applicators working with strawberries to 79 $\mu\text{g/kg-day}$ for mixer/loaders associated with aerial applications on almonds. Combined potential annual occupational and dietary exposures to benomyl ranged from 1.7 $\mu\text{g/kg-day}$ for several work categories to 4.6 $\mu\text{g/kg-day}$ for field workers associated with wine grapes. Combined lifetime average daily dietary and occupational dosages ranged from 1.7 $\mu\text{g/kg-day}$ for several work categories to 3.2 $\mu\text{g/kg-day}$ for field workers associated with wine grapes.

Risk Characterization- The margins of exposure (MOEs) for mean potential daily exposure to benomyl, based on a critical NOEL of 15 mg benomyl equivalents/kg-day for post-implantation loss, ranged from 225 for mixer/loaders involved in aerial applications to almond groves to 10,000 for ground applications of benomyl on strawberries. MOEs for annual occupational exposure to benomyl ranged from 3,000 for field workers with wine grapes to 300,000 for airblast applicators working with stone fruits. The maximum likelihood estimates of excess lifetime risks of cancer ranged from 0.1×10^{-6} for airblast applicators working with stone fruits to 4×10^{-6} for field workers with grapes based on a $q_1 = 0.0028 \text{ (mg/kg-day)}^{-1}$ for hepatocellular adenomas and carcinomas in mice. The 95th upperbound estimate of the excess lifetime risk of cancer ranged from 0.1×10^{-6} to 6×10^{-6} based on a q_1^* of $0.0043 \text{ (mg/kg-day)}^{-1}$ for these same work tasks.

The MOEs for potential daily dietary exposure to benomyl ranged from 342 to 1,300. The MOEs for annual dietary risk from the annualized daily dosage of benomyl ranged from 3,000 to 14,000. The maximum likelihood estimate of the excess lifetime risk of cancer for the U.S. Population was 5×10^{-6} . The 95th upperbound estimate of the excess lifetime risk of cancer for the U.S. Population was 8×10^{-6} .

MOEs for potential combined daily exposure to benomyl ranged from 165 mixer/loaders involved in aerial applications on almonds, to 1,000 for ground application on strawberries. MOEs for potential combined annual exposure ranged from 2,100 for field workers in wine grape vineyards, to 6,000 for several work categories. Maximum likelihood estimates of excess lifetime risks of cancer from combined occupational and dietary exposures ranged from 4×10^{-6} to 9×10^{-6} . The upperbound estimate of the lifetime risk of cancer ranged from 7×10^{-6} to 14×10^{-6} .

Conclusions

Occupational

Margins of exposure, based on current toxicity data, for mean daily occupational exposures were greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. When the mean short term occupational exposures were combined with potential daily dietary exposure, the MOEs still remained greater than 100.

Margins of exposure for annual occupational exposure, or combined occupational exposure and potential annual dietary exposure, were greater than 100. Maximum Likelihood Estimates (MLEs) of excess lifetime risks of cancer from occupational exposure to benomyl ranged from 0.1×10^{-6} to 4×10^{-6} , with 95th percentile upper bounds ranging from 0.1×10^{-6} to 6×10^{-6} . MLEs of excess lifetime risks of cancer from combined occupational and potential annual dietary exposure to benomyl ranged from 4×10^{-6} to 9×10^{-6} , with the 95th percentile upper bounds ranging from 7×10^{-6} to 14×10^{-6} .

Dietary

The margins of exposure for potential daily and annual dietary exposure all population subgroups were greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. The maximum likelihood estimate of the excess lifetime risk of cancer for the U.S. Population was 5×10^{-6} , with a 95th percentile upperbound estimate of 8×10^{-6} .

Tolerances

Seven of the USEPA tolerances for benomyl on agricultural commodities provided margins of exposure less than 100 for theoretical daily dietary exposure to one or more population subgroups if commodities are consumed with residues at the tolerance level. Benomyl has adverse pre-natal effects, which should be taken into consideration when USEPA reviews the tolerance levels under the Food Quality Protection Act.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Benomyl (methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate; CAS #17804-35-2) is a systemic fungicide used to control a wide range of fungal diseases of fruits, nuts, vegetables, field crops, turf, and ornamentals. Benomyl retards or prevents fungal proliferation by interfering with microtubule formation (Davidse and Flach, 1977). This action could inhibit cellular processes dependent upon microtubule formation, such as development and maintenance of cell shape, intracellular transport, and chromosome movements during cell division (Olmsted and Borisy, 1973). Although both plant and mammalian microtubule formation have been reported to be less sensitive than fungi to benomyl (Ireland *et al.*, 1979), certain mammalian functions involving rapid cell proliferation, such as embryological organ development and spermatogenesis, are dependent upon microtubulin. Benomyl entered the risk assessment process because of teratogenicity, oncogenicity, reproductive toxicity, and adverse effects on the liver caused by chronic exposure.

The principal metabolite of benomyl is methyl 2-benzimidazolecarbamate (MBC). This compound, which may be responsible for most of the toxicity of benomyl (Lim and Miller, 1997), is in itself a fungicide; carbendazim (CAS #83601-81-4). Carbendazim has not been registered for use in California since 1989, although it is still registered with the USEPA.

B. REGULATORY HISTORY

In December 1977, the USEPA initiated a Special Review because of possible mutagenic, teratogenic, male reproductive toxicity, and environmental effects. In its final regulatory decision, issued in October, 1982, the Agency added possible oncogenic effects to the list of adverse effects, but determined that the benefits from using benomyl outweighed the risks. The continued use of benomyl was permitted provided that certain exposure reduction procedures were followed (USEPA, 1982). Currently, USEPA considers benomyl a category C (possible human) oncogen with a q_1^* of 4.2×10^{-3} (USEPA, 1987a).

C. TECHNICAL AND PRODUCT FORMULATIONS

Sixteen products containing benomyl are registered in California. Products formulated as dry flowables serve most of the agricultural uses, although wettable powders (50% benomyl) are still available. Home garden products are formulated as 50% wettable powders. Benomyl is also used in three post-harvest applications on fruits. Sprays for crops are applied at rates of 2 oz to 1 lb. a.i./acre, with pre-harvest intervals of 1 to 4 weeks. The recommended rate for applications on turf and mushrooms is 5.4 lb. formulation/acre. The pre-harvest interval for mushrooms is 2 days. A dry flowable formulation was registered in 1987, with labeling oriented to large-scale aerial, ground boom or airblast spraying. Benomyl is also used as a seed treatment and a bulb dip. The dips contain 2 oz to 1 lb. a.i./100 gal.

D. USAGE

The amounts of benomyl used in California in 1990, 1991, 1992, 1994 were 233,000 lb., 124,000 lb., 146,000 lb., and 152,000 lb., respectively. Principal uses were on almonds, grapes, nectarines, peaches, and strawberries (DPR, 1996). Other reported applications involved a wide variety of crops as well as for structural pest control.

E. ILLNESS REPORTS

From 1982 to 1991, several illnesses or injuries have been reported associated with the use of benomyl (Table 1).

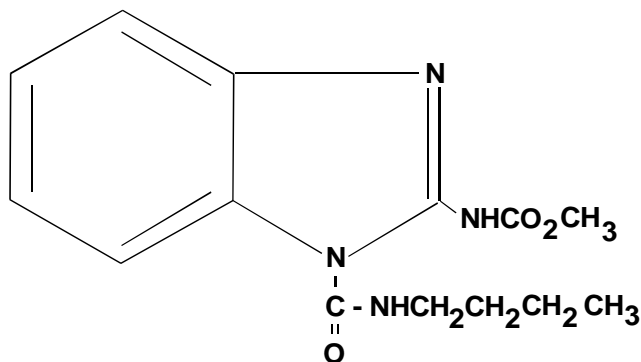
Table 1. Definite and/or probable illness incidents associated with the use of benomyl from 1982 to 1995 (Mehler, 1997)

<u>Activity</u>	<u>Systemic</u>	<u>Eye Injury</u>	<u>Dermal Problems</u>
Ground Applicator	3	6	11
Hand Applicator	3	4	2
Mixer/Loader	3	3	1
Packing/Processing	1	1	1
Exposure to Residue	-	2	7
Drift	2	1	1
Non-Occupational	4	-	-
Totals	16	17	23

Reported clusters of birth defects involving anophthalmia in the United Kingdom were initially associated with the flower industry and the use of benomyl. As high concentrations of benomyl cause this type of terata in laboratory animals (see Developmental Toxicity section), this tended to focus some American public concern regarding the use of benomyl. However, extensive epidemiological investigations of the original reports do not support a cause-and-effect relationship between the use of benomyl and instances of human anophthalmia (Spagnolo *et al.*, 1994; Kristensen and Irgens, 1994; Bianchi *et al.*, 1994).

F. PHYSICAL/CHEMICAL PROPERTIES ^a

Structural Formula:



Molecular weight: parent 290.3; MBC 191.3

Description: White crystalline solid

Melting point: Decomposes without melting

Vapor Pressure: 3.5×10^{-8} mm Hg @ 25°C

Henry's Law Constant $<5.0 \times 10^{-9}$ atmosphere-m³ @ pH7

Solubility:	<u>(mg/L @ 25°C)</u>
Water	0.2
Chloroform	9,400
Dimethylformamide	5,300
Acetone	1,800
Heptane	40

a/ DuPont, 1970; Barefoot, 1988; Hoffman, 1988.

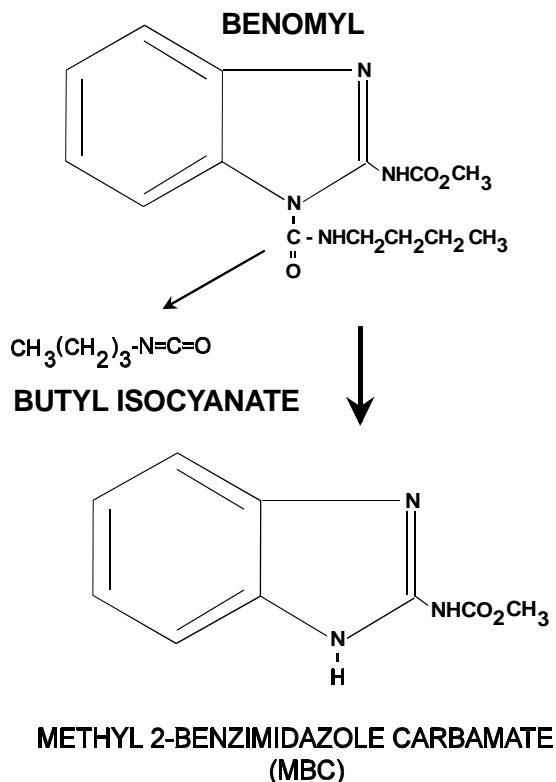
G. ENVIRONMENTAL FATE

Summary- Photolysis is not a significant contributor to the degradation of benomyl. Under light or dark conditions, the half-life of benomyl in buffered (pH 5) solutions was 3-4 hours. In the field, the half-life of benomyl was 3 days. The principal degradation products of benomyl were methyl 2-benzimidazolecarbamate (MBC) and a volatile compound, *n*-butyl isocyanate. In water, *n*-butyl isocyanate rapidly hydrolysed to butylamine and carbon dioxide, with a half-life of 13.8 minutes. The half-life of MBC under aerobic conditions in non-sterile soil was 320 days. Under anaerobic conditions, the half-life of MBC was 743 days. Under field conditions, the half-life of MBC ranged from 51 to 83 days, depending upon soil type and weather conditions. Because of low water solubility and immobility in soil, benomyl and MBC are unlikely to become groundwater contaminants.

Photolysis

Photolysis of [phenyl-¹⁴C(U)] benomyl at 1 ppm was studied in a sterilized solution buffered to pH 5 (Powley, 1985). In natural sunlight, the half-life of benomyl was 4 hours. In the dark, the half-life was 3 hours. The degradation products were identified as methyl 2-benzimidazolecarbamate (MBC) and 3-butyl-2,4-dioxo[1,2-a]-s-triazinobenzimidazole (STB), 99% and 1%, respectively, under both conditions. A volatile, leaving group from the breakdown of each molecule of benomyl is *n*-butyl isocyanate.

Figure 1. Photolysis of benomyl.



[Phenyl-¹⁴C(U)] benomyl was applied to Keyport silt loam soil samples at a rate of approximately 1 lb a.i./acre (Monson and Hoffman, 1990). Fifty percent of the samples were exposed to sunlight, while the others were kept in the dark. At 25°C, the half-life for irradiated samples was 5.2 hours, and non-irradiated samples had a half-life of 5.7 hours. This indicates that photolysis is not a significant contributor to the degradation of benomyl.

Hydrolysis

The hydrolysis of [phenyl-¹⁴C(U)] benomyl was studied in sterilized aqueous solutions buffered at pH 5, 7, and 9 maintained at 25°C in the dark (Wheeler, 1985). The decomposition of benomyl solutions was monitored over 30 days. In pH 5 buffer, the major hydrolysis product was MBC, while at pH 7 and 9, MBC and 3-butyl-2,4-dioxo-[1,2-a]-s-triazinobenzimidazole (STB) were the major hydrolysis products. After 30 days, STB represented approximately 25% of the total radioactivity in pH7 buffer, while in pH9, the STB comprised approximately 80% of

the total radioactivity. The half-lives of benomyl in the pH 5, 7, and 9 buffered solutions were approximately 3.5, 1.5 and less than 1 hour, respectively.

Anaerobic Metabolism

[Phenyl-¹⁴C(U)] benomyl at 1 ppm, which is equivalent to the expected soil residues in the first 10 cm of topsoil when benomyl is applied to a field a 1 lb active ingredient (a.i.)/acre, was incubated in flasks with pond sediment and pond water in the dark at 25°C for 0, 7, and 14 days, and 1, 2, 4, 9, and 12 months (Arthur *et al.*, 1989). Benomyl underwent rapid hydrolysis to MBC. The half-life of MBC under anaerobic conditions was 743 days.

Aerobic Metabolism

Sterile and non-sterile samples of Keyport silt loam soil were treated with [Phenyl-¹⁴C(U)] benomyl at 7 ppm and incubated in the dark at 25°C for 2 hr, 5 hr, and 1,3, 7, 14, 30, 60, 120, 270, and 365 days (Marsh and Arthur, 1989). The half-life in non-sterile soil was 19 hours, but the half-life in sterile soil could not be determined. The principal metabolite was MBC. The half-life of MBC under non-sterile aerobic conditions was 320 days. In sterile soil the half-life of MBC was approximately 1,000 days.

Field Dissipation

Benlate® 50 DF Fungicide was applied to a test site of turf on loam and sandy loam soil in Madeira, California in two applications 14 days apart at a rate of 11 lb a.i./acre per application (McNally, 1990a). Samples were collected at 6 hours, 13, 29, 60, 90, 120, 211, 272, 361, and 541 days after the last application. Benomyl degraded to MBC with a half-life of 3 days. The half-life of MBC was 82.9 days. Throughout the course of the 541 day dissipation study, residues of benomyl were found only in the top 10 cm. The data support the USEPA characterization of benomyl as a Class 1 pesticide, immobile in soil. Thus, benomyl is unlikely to become a groundwater contaminant.

Benlate® 50 DF and carbendazim (80% MBC) were applied to test sites of turf on loam and sandy loam soil in Madeira, California, and to sand in Florida in two applications 14 days apart at a rate of 11 lb a.i./acre per application (McNally, 1990b). Samples were collected at 15, 30, 60, 90, 120, 180, 270, 360, and 540 days. The half-life of benomyl degrading to MBC was 3 days in all locations. The half-life for MBC in sandy soil in Florida was 51.3 days. The average half-life of MBC on the two soil types in California was 67 days.

Less information is available regarding the fate of the other major metabolite of benomyl, *n*-butyl isocyanate. The vapor pressure of *n*-butyl isocyanate is $1.76 \times 10^{+1}$ (Daubert and Danner, 1989). In water, *n*-butyl isocyanate rapidly hydrolysed to butylamine and carbon dioxide (Ulrich, 1989). The half-life of *n*-butyl isocyanate in water was 13.8 minutes (Moye *et al.*, 1978). There have been no direct measurements of the half-life of *n*-butyl isocyanate under field conditions. It has been estimated, based on experimentally derived generic chemical coefficients (Bidleman, 1988; Meylan and Howard, 1991), that *n*-butyl isocyanate would have a half-life of 4.3 days (HSDB, 1999).

TOXICOLOGICAL PROFILE

A. PHARMACOKINETICS

Summary- Benomyl was rapidly metabolized in mammals via hydroxylation and ester hydrolysis in the liver to 2-benzimidazolecarbamic acid methyl ester (MBC) and to methyl 5-hydroxy-2-benzimidazolecarbamate (5-HBC). Neither benomyl, nor MBC accumulated in any body tissues. Approximately 85% of an oral dose of radiolabeled benomyl was excreted in the urine of a rat. As these data were derived from a single animal, the 85% absorption of benomyl was not considered significantly different from 100% oral absorption. Likewise, the oral absorption of MBC, calculated as 85% from urinary data in a small number of animals, was considered to be not different from 100%. Approximately 56% of an oral dose was excreted in the urine of mice, rabbits and sheep. Elimination of MBC and benomyl was primarily via the urine, and was 95% complete 96 hours after oral administration, or 24 hr. after intravenous administration. The amount of benomyl absorbed dermally by rats ranged from 0.03% to 3.5%, depending upon the duration and the amount applied to the skin. Approximately 95% of the dermally absorbed dose was excreted in the urine, with 4% excreted in the feces. None of the submitted or published studies addressed the metabolic fate of *n*-butyl isocyanate in mammals.

Oral and Intravenous- Rat

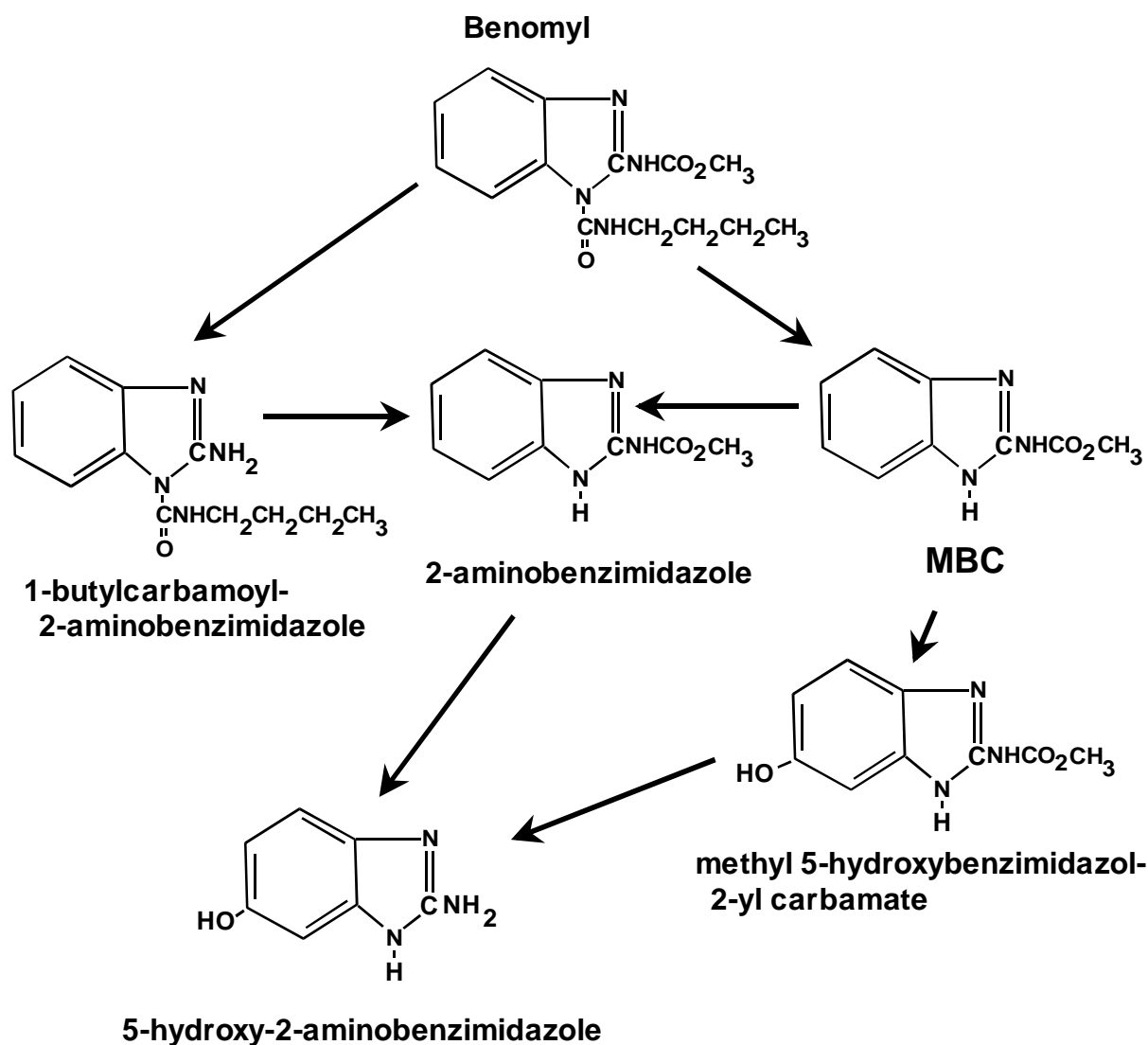
¹⁴C-Carbendazim (benz[2-¹⁴C]imidazolecarbamate) (MBC; 5.7 Ci/mol, 98% purity) was given to adult male albino rats, either orally at 12 mg/kg or intravenously at 12 mg/kg (Krechniak and Klosowska, 1986). The disappearance of MBC followed the kinetics of a two compartment open system model after *i.v.* administration. The apparent volume of distribution greatly exceeded the volume of total body water, suggesting that MBC is bound to extravascular tissues. The composition of the measured radiolabel in the plasma 12 hours after *i.v.* injection was 94% methyl 5-hydroxy-2-benzimidazolecarbamate (5-HBC) and 3% as 2-aminobenzimidazole (2-AB), with only 3% as the unchanged MBC. Urine was the major route of excretion, with 71% eliminated through this route after the rapid phase (half-life, 1.37 hours). The extent of bioavailability of orally administered MBC, calculated by the author from urinary excretion data, was 85%. The composition of metabolites in excreted urine after oral dosing was the same as that following *i.v.* administration. During the rapid phase (half-life of 2.5 hours) following oral dosing, 91% of the compound was eliminated.

Oral- Rat, Dog, Cow, Chicken

[2-¹⁴C]-Benomyl (99% purity, 3.24 μ Ci/mg; 7.7 mg) was administered to a single Charles River CD rat by gavage (Gardiner *et al.*, 1974). After 24 hours, 78.9% of the administered radiolabel was recovered in the urine and 8.7% in the feces. At the end of 48 hours, 85.3% had been recovered in the urine and 12.2% in the feces. After 72 hr, 85.8% had been recovered in the urine and 13.1% in the feces. The same pattern was seen with an oral dose of radiolabeled MBC. As the percentage of radiolabel recovered in the urine and feces was approximately the same at 24, 48, and 72 hours, enterohepatic recirculation does not appear to be of significance. The radiolabeled material in the feces probably represents unabsorbed material. The principal metabolite in the urine was identified as 5-hydroxy-2-benzimidazolecarbamate. Less than 5% of the parent compound was found in the urine. The dog (one animal) responded differently to a bolus oral dose of [2-¹⁴C]-benomyl. Approximately 16% of the oral dose was excreted in the urine, but 83% was excreted in the feces.

Radioactivity did not concentrate in any of the tissues in either the rat or the dog. A chicken and a cow were dosed with radiolabeled material to determine if benomyl concentrated in edible tissues, eggs, or milk. Neither benomyl, nor its metabolites concentrated in any edible tissues in cattle or chickens, or in the milk or eggs.

Figure 2. Metabolism of benomyl in laboratory animals.



Dermal and Intravenous- Rat

Male Charles River CD rats (4 rats/treatment and time interval) were exposed to 2-¹⁴C Benlate® 50 (50% a.i. in a wettable powder; S.A. 1.642 μ Ci/mg) dermally at 0.1, 1, 10, or 100 mg benomyl for 0.5, 1, 2, 4, or 10 hours (Belasco *et al.*, 1981). For intravenous exposure, six rats were injected in the tail vein with either 1 or 10 μ g of radiolabeled material, and terminated at 6, 12, or 24 hours after injection. Dermally absorbed benomyl was rapidly metabolized (principally to methyl 5-hydroxy-2-benzimidazolecarbamate and methyl 2-benzimidazolecarbamate). The amount absorbed through the skin varied depending upon the amount applied and the duration of application. After 4 hours of dermal exposure, the amount absorbed was 1.7% (0.1 mg), 0.3% (1 mg), 0.04% (10 mg), and 0.03% (100 mg). After 10

hours of dermal exposure, the amount absorbed was 3.5% (0.1 mg), 0.5% (1 mg), 0.09% (10 mg), 0.03% (100 mg). Approximately 95% of the dermally administered absorbed dose was eliminated in the urine, and 4% in the feces. Intravenously injected benomyl was eliminated in the urine (approximately 95% of the administered dose in 24 hours) as methyl 5-hydroxy-2-benzimidazolecarbamate, or in the feces (4.1% of the administered dose). No radiolabel was detected in body tissue 24 hours after injection.

Oral and Intraperitoneal- Mouse, Rabbit, Sheep

Male mice (8 weeks of age, 20-25 g body weight), male New Zealand white rabbits (6 weeks, 1 kg body weight), and Romney-Southdown cross wether sheep (26 weeks, 20 kg) were dosed either orally or intraperitoneally with benomyl or MBC at 100 mg/kg (Douch, 1973). Benomyl was rapidly metabolized in mice, rabbits and sheep via hydroxylation and ester hydrolysis in the liver to 2-benzimidazolecarbamic acid methyl ester (MBC) and to methyl 5-hydroxy-2-benzimidazolecarbamate. Following oral gavage, 36%, 34% and 28.4% of the administered benomyl dose was found by the end of the study in the feces of mice, rabbits, and sheep, respectively. Elimination via the urine by the end of the study, was 55%, 56%, and 56% for mice, rabbits, and sheep, respectively. Excretion was 95% complete 96 hr after oral administration in all three species.

Oral and Intraperitoneal- Rat

The effect of benomyl administered orally and intraperitoneally on the activity of hepatic microsomal mixed-function oxidases was examined in male Sprague-Dawley rats (Dalvi, 1992). The activities of several hepatic drug metabolizing enzymes were reduced 24 hours after an intraperitoneal dose of 100 mg/kg. A similar reduction was noted following an oral dose of 500 mg/kg. The *in vivo* inhibition of drug metabolism was demonstrated by increase pentobarbital sleeping time. No alterations were found in the level of serum sorbitol dehydrogenase (a very sensitive indicator of liver damage) 24 hours after either dose.

B. ACUTE TOXICITY

The acute toxicities of technical benomyl and MBC are listed in Table 2.

Table 2 - Acute toxicity of benomyl and methyl 2-benzimidazolecarbamate (MBC) in laboratory animals.

Route/ Species	Sex	Results	Reference
TECHNICAL BENOMYL			
Oral LD ₅₀			
Rat	M	>10,000 mg/kg	1
	F	>10,000 mg/kg	1
Dermal LD ₅₀			
Rabbit	M/F	>10,000 mg/kg	2
Inhalation LC ₅₀ (4 hr)			
Rat	(M/F)	> 2 mg/L	2
TECHNICAL MBC			
Oral LD ₅₀			
Rat	M	>11,000 mg/kg	3
	M	>17,000 mg/kg	4
	M/F	>10,000 mg/kg	5
Guinea Pig	M/F	> 5,000 mg/kg	6
Intraperitoneal LD ₅₀			
Rat	M	>2,000 mg/kg	7
Inhalation LC ₅₀ (1 hr)			
Rat	M	>5 mg/L	8

References- 1. Sherman, 1969a; 2. duPont, 1970; 3. Sherman, 1965; 4. Sherman and Krauss, 1966; 5. Goodman, 1975a; 6. Hinckle, 1981; 7. Goodman, 1975b; 8. Sarver, 1975.

The observed clinical signs following acute exposure of rats to benomyl were liquid stools, and urine-stained fur (Foss, 1993). Technical benomyl caused a Category III reaction (corneal involvement or irritation for 1-7 days) in the primary eye irritation test (Frank, 1968). None of the dermal irritation nor sensitization studies were acceptable to DPR under FIFRA guidelines.

C. SUBCHRONIC TOXICITY

Summary- In subchronic studies, the principal toxic effects of benomyl or MBC were on the germinal epithelium of the testes, and the liver. In a 70-day subchronic study, the NOEL for a single oral dose of benomyl causing sloughing of portions of the germinal epithelium in seminiferous tubules of male rats was 25 mg benomyl/kg. Rat seminiferous tubular atrophy and efferent ductal occlusions persisted at least 70 days after a single oral dose of 100 mg benomyl/kg, or greater. The 85-day NOEL for fertility in rats was 100 mg benomyl/kg-day. The 7-day lowest observed effect level (LOEL) for hepatic toxicity (portal congestion) in rats was 40 mg benomyl/kg-day.

Diet- Rat

Male Wistar rats (9/dose) 25-28 days of age, were fed on a diet containing benomyl (purity unstated) at 0, 40, 80, 165, 200, 240, 280, 320, 360, 400, 440, 480, 520, 560, or 600 mg/kg-day for seven days (Igbedioh and Akinyele, 1992). Histopathological findings included cellular swelling and edema of the liver, kidney, and spleen. There was a dose dependent increase in the incidence and severity of the liver changes, ranging from mild portal congestion at 40 mg/kg-day to widespread vascular degeneration of hepatocytes and necrosis at 600 mg/kg-day. The LOEL was 40 mg/kg-day. The data were considered supplemental.

Gavage- Rat

Technical benomyl (purity unknown) at 0, 200, or 400 mg/kg-day was administered by gavage, 5 days per week for two weeks to male Sprague-Dawley rats (4-6/treatment group) (Carter and Laskey, 1982). These dosages produced a 35-48% reduction in epididymal and vas deferens sperm counts, as determined 14 days after treatment. The data were considered supplemental.

Twenty-one day old, male Long-Evans rats (n = 12, 8, 8, 8, 7 for the respective doses) were given MBC (98.1% purity) in corn oil at 0, 50, 100, 200, or 400 mg/kg-day by oral gavage for 85 days (Goldman *et al.*, 1989). Fertility was assessed by pairing treated males with females for 20 days. Failure to produce viable offspring following this period of pairing was considered as an indication of infertility. The NOEL for fertility was 100 mg/kg-day. Serum follicle stimulating hormone (FSH) was significantly ($P < 0.05$) elevated at the high dose, but serum levels of luteinizing hormone (LH), prolactin, and thyroid stimulating hormone (TSH) were not affected. The data were considered supplemental.

Male Sprague-Dawley rats (8/dose/termination time), 33 days old, were given technical benomyl (purity unknown) at 0, or 200 mg/kg-day by gavage, 5 days per week for two weeks (Carter, 1982). The animals were terminated at intervals of 3 to 59 days after cessation of dosing. There were no reported changes in sperm concentration in the vas deferens, or in total epididymal sperm. There were no reported changes in testicular histology as determined by immersion fixation. The data were considered supplemental.

MBC (98.1% purity; 1.9% inerts) at 0 or 400 mg/kg-day was administered by gavage to 90-day old male Charles River rats (23-24/group), 5 days/week for two weeks (Carter *et al.*, 1987). The male rats were proven breeders, and were placed with 1 female for 1 week on day 3 of treatment. Females were replaced weekly with nulliparous females for 32 weeks after termination of treatment. All males were killed at week 35 post exposure, and testicular tissues were examined. Females were terminated 12 days after the breeding period. Uterine contents were examined. At termination, testicular weights in treated males were 39% less than controls. Testicular weights of totally infertile males were 58% less than controls. Some of the treated males (10/24) failed to produce a pregnant female in the first week after treatment. By week five, 16/24 males were infertile, and 12 remained infertile throughout the study. Histopathology indicated atrophic seminiferous tubules lined with Sertoli cells, but few germinal cells undergoing spermatogenesis. The study was considered supplemental information.

Technical benomyl (purity unknown) at 0, 125, 250, 500, or 1,000 mg/kg-day was administered by gavage to 33-day, 54-day, and 75-day old male Sprague-Dawley rats (5/interval/dose) for 5 days divided into two dosings per day (Carter *et al.*, 1984). Blood samples were taken at 29 days after treatment, and animals were terminated 31 days after treatment. No significant effects on male reproductive parameters were noted in pre-pubescent (33-day) rats. Epididymal sperm counts were reduced in pubescent rats (54-day). Post-pubescent rats demonstrated a wide variability in sperm counts with treatment. Histological exams of testicular tissue revealed an increased incidence of diffuse hypospermatogenesis in the seminiferous tubules of pubescent and post-pubescent male rats with increasing dose. The data were considered supplemental.

A benomyl formulation (50% benomyl with 50% inerts) at 0 or 200 mg formulation/kg-day was given by gavage to adult male Charles River CD rats (5/group) in 10 doses (Dashiell, 1978). The males were each mated with two females three days after the last dose, and a second time at 59 days after the last dose. In the first mating, nine out of ten females mated with control males became pregnant, but only three of ten females mated with treated males became pregnant. At 59 days, there was no difference in the success rate of controls (9/10) and treated (10/10). In the second part of the experiment, male rats (5/group/termination time) were dosed in the same manner and terminated at 4 hours, 14, 28, 42, 70, and 90 days post dosing. Benomyl had no significant effect on testicular weight at any of the varying periods of time. However, microscopic lesions were noted in the testes. The lesions ranged severity between focal to diffuse degeneration of the germinal epithelium, accompanied by giant cells, occasional sperm granulomas and reduction or absence of sperm. The data were considered supplemental.

Adult male Sprague Dawley rats (100 days of age) were given single oral doses of benomyl (95% purity) at 0, 25, 50, 100, 200, 400, or 800 mg/kg and terminated at 2 or 70 days post-treatment to determine the chemical effects of benomyl on spermatogenesis and the epididymis (Hess *et al.*, 1991). Testes were fixed via vascular perfusion with 3% glutaraldehyde in 0.05 M cacodylate buffer, pH 7.3. Fifty sections were examined from each testis. Sloughing of germ cells was observed at each dosage by the second day. Data were reported on a per/animal basis (0/8 for controls, 1/8 at 25 mg/kg, 4/7 at 50 mg/kg, 12/15 at 100 mg/kg, 7/8 at 200 mg/kg, 8/8 at 400 mg/kg, and 8/8 at 800 mg/kg). Sloughing of the germinal epithelium is an indication of reduced sperm production and potential infertility (Dashiell, 1978; Carter *et al.*, 1984, 1987; Mebus, 1991). Because just one affected tubule on one section caused an animal to be classified as affected, and there were no data on the percentage of tubules/animal which were affected in this study, the severity of the response could not be estimated. The ratio of the number of animals affected to the number of animals treated at the 25 mg/kg was not significantly different from that of the controls. Consequently, the single-dose NOEL for sloughing of the germinal epithelium was determined to be 25 mg/kg. At 70 days, mean testicular weight and tubular diameters were reduced only at the highest dosage, but tubular atrophy and efferent ductal occlusions were found as low as 100 mg/kg. The data were considered supplemental.

Inhalation- Rat

CD rats (20/sex/group) were exposed to atmospheric concentrations of benomyl (purity unknown) at 0, 10, 50, or 200 mg/m³ via nose only for 6 hours a day, 5 days a week for up to 90 days (Warheit *et al.*, 1989). Half of the rats were terminated at 45 days, and the remaining animals at 90 days. Female rats exhibited a significant (P<0.05) dose dependent decrement in body weight gain (27-48%) during the last 30 days of the study. At 45 days, all of the males and 8/10 females at 200 mg/m³, and 2/10 males at 50 mg/m³ exhibited mild degeneration of the olfactory epithelium. At 90 days, all rats at 200 mg/m³, and 3 males at 50 mg/m³ exhibited degeneration of the olfactory epithelium. Histopathological examination of the testes at 90 days revealed 2/10 males with depletion of the spermatid layer at 200 mg/m³, and 1/10 with degeneration of the germinal epithelium at 50 mg/m³. The NOEL for histopathological changes in the olfactory epithelium was 10 mg/m³. The data were considered supplemental.

The toxicity of a volatile breakdown product of benomyl, *n*-butyl isocyanate, was examined in rats in a published study. Male Wistar rats (20/dose) were exposed via nose only to *n*-butyl isocyanate (99.5% purity) at concentrations of 0, 1.1, 6.2, 15 or 26 mg/m³ for 6 h/day for 5 days (Pauluhn and Eben, 1992). Measurements were continued for 3 weeks post exposure. No treatment related clinical signs were observed at 1.1 or 6.2 mg/m³. Rats exposed to 15 mg/m³ appeared unkempt and exhibited labored breathing, reduced motility and increased serous discharge from the nose. At the high dose, 12/20 rats died between days 10 and 15 after exhibiting severe respiratory distress, reduced motility, lethargy, unkempt fur, serous discharge from the nose, perinasal wetness, and cyanosis. All other rats survived the exposure regimen. At the end of the observation period, rats exposed to 6.2 and 15 mg/m³ were hyperresponsive to an acetylcholine bronchoprovocation aerosol. Biochemical and cellular components in broncho-alveolar lavage fluid (BALF) from rats at the three high doses indicated a concentration dependent and protracted increase of polymorphonuclear leukocytes and further inflammatory parameters. BALF parameters were not affected at mg/m³. The NOEL for significant effects in BALF parameters was 1.1 mg/m³.

Diet- Dog

In a range-finding study, beagle dogs (4/sex/dose) were fed on a diet containing benomyl (51.5% purity) at 0, 100, 500, or 2,500 ppm active ingredient (approximately 0, 3.5, 17.7, or 84 mg/kg-d for males; 0, 4.2, 19.1, or 84 mg/kg-d for females from consumption data) for 90 days (Sherman, 1968a). There were no nutritional, clinical, urinary, pathologic, or hematological changes attributable to exposure to benomyl. Elevated levels of alkaline phosphatase (152%) and serum glutamic-pyruvic transaminase (159%), and a decrease in the albumin/globulin ratio (34%) were noted in female dogs at the high dose. These changes in blood chemistry were considered to be indications of an effect on the liver. The study was considered supplemental.

D. CHRONIC TOXICITY/ONCOGENICITY

Summary- Neither benomyl, nor MBC were oncogenic in rats, but both compounds caused hepatocellular adenomas and carcinomas in several strains of mice. The principal non-oncogenic effect of chronic exposure to benomyl or MBC was hepatotoxicity. In one dog study, the 2-year NOEL for hepatotoxicity (histopathological and clinical chemistry changes) in the female dog was 2.6 mg MBC/kg-day. In the study in which dogs were dosed with benomyl for two years, the NOEL for changes in clinical chemistry indicating hepatotoxicity was 15 mg/kg-day. The 2-year NOEL for hepatotoxicity (pericholangitis/ cholangiohepatitis) in the rat was 4.9

mg MBC/kg-day. The NOEL for hepatotoxicity (centrilobular hypertrophy, single cell necrosis with reparative mitotic activity, increased pigment storage in Kupffer cells, occasional scar formation, and increased liver weights) in the mouse was 23 mg MBC/kg-day. The NOEL for testicular germ cell atrophy and sperm stasis in the mouse was 75 mg MBC/kg-day.

Diet- Dog

Beagle dogs (4/sex/dose) were fed on a diet containing benomyl (50% purity with 50% excipients) at 0, 100, 500, or 2,500 ppm (0, 3, 15, 75 mg/kg-day based on a default value of 1 ppm = 0.03 mg/kg-day; Zielhuis and van der Kreek, 1979) for two years (Sherman, 1970). There was histological evidence of cirrhosis of the liver at 2,500 ppm. Blood levels of cholesterol, alkaline phosphatase, and serum glutamic-pyruvic transaminase were significantly ($P < 0.05$) elevated in males at 2,500 ppm. The NOEL for hepatotoxicity was 15 mg/kg. There was testicular atrophy at the 15 and 75 mg/kg-day. Two of four males exhibited mild focal testicular degeneration. Although a relationship of testicular atrophy to the test compound was initially suspected, it could not be confirmed in later studies (Sherman, 1972a; Stadler, 1986) and was ultimately considered not chemically related. After several supplemental submissions of data, the study was considered acceptable to DPR under FIFRA guidelines (USEPA, 1984; Aldous, 1996).

Male and female beagle dogs (4/sex/dose) were fed on a diet containing MBC (as a 53 - 72% formulation) at 0, 100, 500, or 1,500 - 2,500 ppm MBC (approximately 0, 2.7, 13.5, or 62.7 mg/kg-day for males and 0, 2.6, 14.1 or 49 mg/kg-day for females based on dietary consumption data) for two years (Sherman, 1972a). After one year of continuous feeding one male and one female dog from the control group, one female and one male from a mid-dose group (500 ppm) and one female from the high dose group were terminated for histopathologic evaluation. In addition, one male dog from the high dose group was terminated in extremis after 42 weeks. No clinical signs of toxicity were observed at the two low doses. At the high dose, the dogs' food consumption was severely reduced, and did not respond to appetite enhancers. MBC was hepatotoxic at the highest dose in both male and female dogs causing hepatic cirrhosis, hepatic inflammation, and fatty liver (Table 3). Significant ($P < 0.05$) elevations of cholesterol (65% in males but not females), alkaline phosphatase (79% in males and 103% in females), and SGPT (198%-667% in males and 145%-1,118% in females) were noted at various time points from 1 month to two years in the high dose group. At 500 ppm, cholesterol (32% in males) and alkaline phosphatase (38% in males and 53% in females) were elevated at various times, but SGPT was not. The NOEL for hepatotoxicity in females was 100 ppm (approximately 2.6 mg/kg-day). The study was unacceptable to DPR under FIFRA guidelines due to a lack of dietary analysis and absence of ophthalmoscopic examinations.

Table 3 - Histopathological changes in the livers of dogs dosed with MBC in the diet for up to two years (Sherman, 1972a).

Parameter	Males				Females			
	0 mg/kg-d	2.7 mg/kg-d	14 mg/kg-d	63 mg/kg-d	0 mg/kg-d	2.6 mg/kg-d	14 mg/kg-d	49 mg/kg-d
fatty liver	0/4	0/4	0/4	1/4	0/4	0/4	1/4	2/4
hepatic inflammation	0/4	0/4	0/4	3/4	0/4	0/4	1/4	1/4
hepatic cirrhosis	0/4	0/4	0/4	3/4	0/4	0/4	1/4	1/4

Beagle dogs (5/sex/dose) were fed on a diet containing MBC (98.8% purity) at 0, 100, 200 or 500 ppm (approximately 0, 2.9, 6.4, 16.5 mg/kg-day for males, and 3.2, 7.2 or 17 mg/kg-day for females based on dietary consumption data) for one year (Stadler, 1986). No clinical signs of toxicity were reported, and there were no histopathological changes reported. In the high dose group, serum levels of cholesterol were slightly elevated in females (20-48%) and males (8-22%). There was a slight decrease in serum albumin levels (11% in females) at 3 months in the 500 ppm group. The NOEL for slight changes in serum cholesterol and serum albumin was 7.2 mg/kg-day. The study was unacceptable to DPR under FIFRA guidelines because there were no ophthalmoscopic exams.

In a two-year dog study reviewed by FAO, body weight was decreased in 300 ppm males, with a no-effect level of 150 ppm (FAO, 1985). The study was considered supplemental information.

Diet- Rat

Benomyl (50-70% active ingredient) at 0, 100, 500, or 2,500 ppm in the feed was fed to CD rats (36/sex/group) for up to two years (Sherman, 1969b). There was no nutritional, clinical, hematological, urinary, biochemical or histopathological evidence of toxicity in the test groups which could be attributed to benomyl. The study was unacceptable to DPR under FIFRA guidelines because there was no indication that a maximum tolerated dose had been reached, there were no ophthalmoscopic exams, and the stability of the test article in the feed was not validated.

MBC (formulated as a 53 - 72% wettable powder) was fed to CD rats (36/sex/dose) at dietary concentrations of 0, 100, 500, or 5,000 ppm, with a fifth group receiving 2,500 for 18 weeks before being increased to 10,000 ppm (Sherman, 1972b). No clinical signs of toxicity were reported. No oncogenic effects were apparent. Hepatotoxicity was indicated by increases of 20-24% in relative liver weight in females dosed with 5,000 and 10,000 ppm. In addition, there was an increased frequency and severity of pericholangitis/cholangiohepatitis, and (at 12, 18 or 24 months) increases in serum alkaline phosphatase (20-50%) and glutamic pyruvic transaminase activity (40-85%) indicating liver damage at 5000-10,000 ppm in both sexes. The NOEL for pericholangitis-cholangiohepatitis in females was 100 ppm (approximately 4.9 mg/kg-day from food consumption data). The study was unacceptable to DPR under FIFRA guidelines due to a lack of ophthalmoscopic examinations, lack of feed analysis, and inadequate group sizes.

Diet- Mouse

CD-1 mice (80/sex/group) were fed on a diet containing benomyl (99% purity) at 0, 500, 1500, or 7500 ppm for 37 weeks (Wiechman, 1982). At 37 weeks the top dosage was dropped to 5000 ppm due to excessive toxicity. The study continued for a total of two years. Non-neoplastic lesions were seen in the liver, skin, thymus, spleen, nasal cavity, and male reproductive tract in the 5000 ppm group. Increased numbers of lymphocytes were reported in the tracheal walls of females dosed with 1500 ppm; however, minimal biological significance was attached to this finding. The NOEL for non-neoplastic effects was 1500 ppm (225 mg/kg-day, as calculated by the default consumption value of 1 ppm = 0.15 mg/kg-day, Zielhuis and van der Kreek, 1979). Hepatocellular adenomas and carcinomas were found, beginning on day 445 in males and day 426 in females (Table 4). This was the only study in mice reporting clear increases in tumors at dosages that were not hepatotoxic. The threshold for hepatotoxicity was also higher than in other studies. The time to tumor expression was not dose-related.

However, the severity of the tumors may have been related to dose as no controls with tumors died before sacrifice, yet, 15 treated females in all dose groups did. Most of the tumors found at termination were multicentric, with a dose-related increase in multiplicity. There was a similar increase in hepatic neoplasms in males at the low and middle dosages, but not at the high dose. As there was evidence of hepatotoxicity in the latter group, it was possible that metabolic conversion to the ultimate carcinogen was impaired. The study was acceptable to DPR under FIFRA guidelines.

Table 4 - Hepatocellular adenomas and carcinomas induced in CD-1 mice at risk^a by dietary exposure to benomyl for up to two years (Wiechman, 1982).

Tumor Type	Dosage (mg/kg-day)				Female Dosage (mg/kg-day)			
	0	75	225	750	0	75	225	750
Hepatocellular adenomas	9/60 (15%)	9/75 (12%)	11/73 (15%)	10/76 (13%)	2/64 (3%)	2/60 (3%)	7/73 (10%)	7/68 (10%)
Hepatocellular carcinomas	16/60 (27%)	26/75 (35%)	41/73** (56%)	17/76 (22%)	2/64 (3%)	7/60 (12%)	6/73 (8%)	14/68** (21%)
Combined Tumor Incidence	25/60 (42%)	35/75 (47%)	52/73* (71%)	27/76 (36%)	4/64 (6%)	9/60 (15%)	13/73* (18%)	21/68** (31%)

a/ The mice at risk were those that lived as long as the earliest detected hepatocellular adenoma or carcinoma (day 445 in males and day 426 in females).

* Significantly different from control (P<0.05) by Fisher's exact test.

** Significantly different from control (P<0.01) by Fisher's exact test.

CD-1 mice (80/sex/dose) were fed on a diet containing MBC (99.3% purity) at dosages of 0, 500, 1500, or 7500 ppm (approximately 0, 75, 225, or 1,125 mg/kg-day as calculated from the default consumption value of 1 ppm = 0.15 mg/kg-day) for up to two years (Wood, 1982). MBC was hepatotoxic, and reduced survival in males at all dosages. The high-dose for males was reduced to 3,750 ppm (approximately 563 mg/kg-day) after 1 year, and the animals were terminated in week 73 when survival was only 29% (vs. 65% in the male controls). A liver lesion [characterized by centrilobular hypertrophy and hepatocyte swelling, focal/multifocal necrosis, and single cell necrosis] was noted in all groups of males. Females had significantly (P<0.05) elevated relative liver weights in the intermediate (31%) and high dose (38%) groups. Hepatocellular tumors were present in treated males and females beginning on day 437 (Table 5). Dose-related reductions in tumor latency, and increases in cellular alterations, tumor prevalence, malignancy, and multiplicity all indicate an oncogenic effect in females. Results in the male groups were inconclusive. Males had a relatively high spontaneous prevalence of adenomas. Compound-induced mortality and hepatotoxicity further complicated the question of whether MBC induced liver tumors in males. While the incidence and multiplicity of hepatocellular neoplasms was increased in the low and intermediate dose male groups, there was no indication that tumor latency was reduced by treatment. Testicular germ cell atrophy (bilateral) and sperm stasis (bilateral) were noted in the high (13/74 and 11/74, respectively) and intermediate (12/80 and 3/80, respectively) dose males compared to controls (7/77 and 0/77, respectively). There was a bilateral accumulation of yellow-brown granular pigment in the renal tubules of high-dose mice, and kidney weights were depressed slightly in high-dose

males. The NOEL was 75 mg/kg-day for histopathological effects on the testes. The study was acceptable to DPR under FIFRA guidelines.

Table 5 - Hepatocellular adenomas and carcinomas induced in CD-1 mice at risk^a by dietary exposure to MBC for up to two years (Wood, 1982).

Tumor Type	Male Dosage ^b (mg/kg-day)			Female Dosage (mg/kg-day)			
	0	75	225	0	75	225	1125
Hepatocellular adenomas	11/70 (16%)	14/64 (22%)	14/61 (23%)	0/68 (0%)	5/62 (8%)*	5/66 (8%)*	3/71 (4%)
Hepatocellular carcinomas	2/70 (3%)	5/64 (8%)	9/61 (15%)	2/68 (3%)	4/62 (6%)	15/66 (23%)*	12/71 (17%)*
Combined Tumor Incidence	13/70 (19%)	19/64 (30%)	23/61 (38%)	2/68 (3%)	9/62 (15%)*	20/66 (30%)*	15/71 (21%)*

a/ The mice at risk were those that lived as long as the earliest detected hepatocellular adenoma or carcinoma (day 437).

b/ High dose group (1125/563 mg/kg) was terminated after one year due to excessive mortality.

* Significantly different (P<0.05) from control by Fisher's exact test.

NMRfK mice (100/sex/dose) were fed MBC (99% purity) at 0, 50, 150, 300 or 1000 ppm for 22 months (Donaubauer, 1982). At 4 weeks the high dose was increased to 2000 ppm, and at 8 weeks the high dose was again increased to 5000 ppm. Liver effects included centrilobular hypertrophy, single cell necrosis with reparative mitotic activity, increased pigment storage in Kupffer cells, occasional scar formation, and increased liver weights. These effects occurred mainly in the high dose group, with marginal effects in the 300 ppm group, giving a NOEL of 150 ppm (approximately 23 mg/kg-day). No hepatocellular carcinomas or hepatoblastomas were reported, although there was some incidence of hepatocellular adenomas (Table 6). Malignant granulosa cell tumors and/or luteomas were also reported. The study was not acceptable to DPR under FIFRA guidelines due to deficiencies in histopathology (only liver, lung, and gross lesions were examined) and lack of individual animal data, but the findings contribute to the overall understanding of the hepatotoxic effects of benomyl/MBC in mice.

Table 6 - Neoplastic lesions in NMRFk mice associated with dietary exposure to MBC for 22 months (Donaubauer, 1982).

Tumor Type	Male Dosage (mg/kg-day)					Female Dosage (mg/kg-day)				
	0	7.5	23	45	750	0	7.5	23	45	750
Hepatocellular adenoma	3/97 ^a (3%)	2/99 (2%)	0/99 (0%)	0/95 (0%)	1/99 (1%)	0/98 (0%)	0/98 (0%)	0/95 (0%)	1/95 (1%)	0/95 (0%)
Granulosa Cell Tumors/luteomas						2/98 (2%)	2/98 (2%)	3/95 (3%)	7/95 (7%)	10/97* (10%)

- a/ Total number of animals examined. In the absence of individual animal data, it was not possible to determine the number of animals which lived long enough to develop tumors.
- * Significantly different (P<0.01) from control by Fisher's exact test.

MBC (99% purity) at 0, 150, 300, or 1,000 ppm (approximately 0, 23, 45 or 150 mg/kg-day as calculated from the default consumption value of 1 ppm = 0.15 mg/kg-day) was fed to Swiss mice (100/sex/dose) for 80 weeks (Beems *et al.*, 1976). The level in the high dose group was increased to 2,000 ppm at week 4, and to 5,000 ppm (approximately 750 mg/kg-day) at week 8. There were cellular alterations in the livers of all treated groups, and morphologic changes consistent with microsomal enzyme induction, such as swollen centrilobular hepatocytes with granular basophilic cytoplasm and large nuclei, in the high dose group. Relative liver weights were 130% of control in the 5,000 ppm males and 120% of control in the 5,000 ppm females. The NOEL for increased relative liver weight was 300 ppm. There were increases in hepatocellular adenomas in treated females, and in relatively rare hepatoblastomas in treated males (Table 7). The latter were tabulated separately, but occurred only within or at the border of an adenoma or carcinoma. They are an anaplastic form of hepatic carcinoma and, having the same cell of origin, they were pooled for risk assessment. The study was considered supplemental information.

Table 7 - Hepatocellular adenomas, carcinomas, and hepatoblastomas induced in Swiss mice by dietary exposure to MBC for 80 weeks (Beems *et al.*, 1976).

Tumor Type	Male Dosage (mg/kg-day)				Female Dosage (mg/kg-day)			
	0	23	45	750	0	23	45	750
Hepatocellular adenomas	9/100 ^a (9%)	6/98 (6%)	13/100 (13%)	9/100 (9%)	0/97 (0%)	1/99 (1%)	1/98 (1%)	9/97** (10%)
Hepatocellular carcinomas	1/100 (1%)	1/98 (1%)	2/100 (2%)	1/100 (1%)	1/97 (1%)	0/99 (0%)	0/98 (0%)	0/97 (0%)
Hepatoblastomas	1/100 (1%)	1/98 (1%)	1/100 (1%)	7/100** (7%)	0/97 (0%)	0/99 (0%)	0/98 (0%)	0/97 (0%)
Combined Tumor Incidence	11/100 (11%)	8/98 (8%)	16/100 (16%)	17/100 (17%)	1/97 (1%)	1/99 (1%)	1/98 (1%)	9/97** (9%)

^{a/} Total number of animals examined. In the absence of individual animal data, it was not possible to determine the number of animals which lived long enough to develop tumors.

** Significantly different (P<0.01) from control by Fisher's exact test.

E. GENOTOXICITY

Summary. Benomyl was not mutagenic in *Salmonella* sp. in three studies, with or without metabolic activation. MBC was positive in two of five studies in bacteria, and in one of three studies using mammalian cells. 5-Hydroxy MBC was negative in one bacterial gene mutation study. Benomyl caused chromosomal aberrations at 1000 mg/kg in mice, and sister chromatic exchanges in CHO cells. MBC was reported to cause spindle effects in HeLa cells. Neither benomyl nor MBC caused an increase in DNA repair in primary mouse or rat hepatocytes. MBC did not produce differential growth inhibition or cytotoxicity in *B. subtilis*.

Taken together, these results suggest that MBC (or an impurity which is not always present) possesses some genotoxic activity.

Gene Mutation- Benomyl

Benomyl (99.2% purity) at 0, 5, 10, 50, 100, 250, 375, 500, or 1,000 µg/plate was incubated with *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, with and without S-9 mouse liver activation (Summers, 1981b). Although there was cytotoxicity above 250 µg/plate, there was no indication of mutagenic activity. The study was acceptable to DPR. The acceptability of the genotoxicity studies was based on the Toxic Substances Control Act guidelines (Federal Register, 1985).

Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 were incubated with benomyl (99% purity) at 0, 10, 25, 50, 100, or 200 µg/plate without activation, and 0, 25, 50, 100, 250, or 500 µg/plate with S-9 rat liver activation, all in duplicate with two trials (Russell and Rickard, 1986a). There was no indication of an increased reversion rate. The study was acceptable to DPR.

Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 were incubated with benomyl (99% purity) at 0, 25, 50, 100, 250, or 500 µg/plate without S-9 rat liver activation, or 0, 25, 50, 100, 250, 500, or 1,000 µg/plate with activation, all in duplicate with two trials (Russell and Rickard, 1986b). Cytotoxicity was noted at the high dose in each trial. There was no indication of an increased reversion rate. The study was acceptable to DPR under TSCA guidelines .

Benlate (50% benomyl) was administered at benomyl concentrations of 0.125 to 5.0 µg/ml to *E. coli* strains WP2_{uvrA}, WP2, CM611, *Salmonella typhimurium* TA1535 and TA1538 (Kappas *et al.*, 1976). A simplified fluctuation test was used. Two assays were positive (WP2_{uvrA}, and TA1535) in the range of 0.125 to 1.0 µg/ml of benomyl. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Benomyl (purity unstated) at 0.25 to 0.40 µg/ml induced reverse mutations from both biotin and pyridoxine requirement in the excision-deficient UT517 strain of *Aspergillus nidulans* (Kappas and Bridges, 1981). There was no detectable mutagenic effect in the repair-proficient UT439. Reverse mutations from adenine requirement in a UV-sensitive strain (UT540) of *Aspergillus nidulans* were also induced. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Benomyl (purity unknown) caused forward mutations, creating monoauxotrophs with several mutant *Fusarium oxysporum* having amino acid requirements (Dassenoy and Meyer, 1973). The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Benomyl (purity unknown) at 0.25 or 0.5 ppm caused increased segregation of *Aspergillus* colonies (diploids distinguishable by color), and many of the colonies produced were haploids (Hastie, 1970). The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Benomyl (purity unknown) at 500 µg/3x5 cm triangle of filter paper was tested for the ability to induce point mutations in *Aspergillus nidulans* with 8-azaguanine resistance (Bignami *et al.*, 1977). There was no increase in mutation frequency. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Benomyl (purity unknown) at 20 or 500 µg/3x2 cm of triangular absorbent paper was not mutagenic to *S. typhimurium* strains TA1535, TA1536, TA1537 or TA1538 in the reverse mutation spot test, with and without activation by Phenobarbital-induced male rat liver (Carere *et al.*, 1978). The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Benomyl (purity unknown) and two of its formulations were tested in various gene mutation assays (Fiscor *et al.*, 1978). The compounds were negative in *in vitro* spot tests, in microsomal plate assays, in liquid-culture treatments, and in the rodent host-mediated assay. The base-pair substitution *S. typhimurium* mutant *hisG46* and the *hisG46*-bearing *uvrB* excision-repair deficient mutants TA100, TA1530, TA1535, or TA1950 were used as the test organisms. Neither benomyl, nor MBC were mutagenic at the dose levels tested. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Benlate® (50% wettable powder) at up to 1200 µg/plate in the absence of rat S9 activation, and up to 750 µg/plate with activation was tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100 (Russell, 1977). There were two replicates per dose level in two separate experiments. All strains were negative with or without S9 activation. The study was unacceptable to DPR under TSCA guidelines because of the test article used.

Benomyl (99.05 and 99.4% purity) at concentrations of 500 µg/plate in the presence or absence of S9 rat liver activation was tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100 (Russell, 1978). There were two replicates per dose level in up to 8 separate trials per strain/treatment/S9 combination. There was evidence that the toxicity was extremely variable between strains and between trials. In most cases, some toxicity was observed in several dose levels in tests without S9 activation. Strain TA1537 without S9 activation had elevated numbers of revertants in several trials and at several dose levels. The study was unacceptable to DPR under TSCA guidelines because of the variability in toxicity which suggested problems in the execution of the study.

Benomyl (99% purity) was tested in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, and in *Escherichia coli* WP2 *hcr* to detect gene mutations (Shirasu *et al.*, 1978). A host mediated assay was done using *Salmonella typhimurium* strain G46 in mice. In addition, a DNA damage/repair study was performed: a *rec*-assay in *Bacillus subtilis* strains M45 and H17. All results were negative. The study was unacceptable to DPR under TSCA guidelines because the dosages were not justified, there were no analyses of dosing solutions, and insufficient individual data for independent analyses.

Benlate® (50% benomyl) at 1 mg/ml, or MBC (purity unknown) at 0.5 mg/ml were dissolved in 0.5% DMSO for testing in *Drosophila melanogaster* (Lamb and Lilly, 1980). Food and water were withheld from adult male [*Oregon-R* strain] flies for 16 hours, then the flies were placed in the presence of a drop of benomyl, MBC, or DMSO. Differences in weights of groups of 5 flies were taken as estimates of consumption. Neither benomyl nor MBC increased the numbers of recessive lethals. Significant increases in numbers of sterile males were noted at a time period corresponding to exposure of pre-meiotic spermatocytes and spermatogonial cells for both benomyl and MBC. No increases in male sterility were noted in *yw+B/B^SYy* males used chromosome loss and breakage tests in the same report.

Benomyl (99.9% purity) at concentrations up to 172 µM with S9 rat liver activation (4 trials), and 805 µM without S9 activation (5 trials) was tested with Chinese hamster ovary cells for mutagenicity (Summers, 1980a). There was not treatment effect on chromosomal aberrations. The study was unacceptable to DPR under TSCA guidelines because of the large variability between trials and the lack of QA/GLP.

Gene Mutation- MBC

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 were incubated with MBC (98% purity) at 0, 10, 50, 100, 500, 1,000, or 3,000 µg/plate in a single trial in duplicate (Shirasu *et al.*, 1977a). There was no indication of an increased reversion rate. The study was unacceptable to DPR under TSCA guidelines .

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 were incubated with 2-benzimidazolecarbamic acid, methyl ester (99.1% purity) at 0, 200, 400, 600, 800, 1,000, 4,000, 8,000 or 10,000 µg/plate, with and without S-9 liver activation (Russell and Rickard, 1986c). There was a positive, concentration dependent response with S-9 activation in

TA1537, TA1538, and TA98 (frame shift), with the revertant frequency greater than twice the background at equal to, or greater than background at 4,000 µg/plate or greater for all three strains. Reversion was significant in TA100 at concentrations between 4,000 and 8,000 µg/plate, but the frequencies were less than twice the background. The study was acceptable to DPR under TSCA guidelines .

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 were incubated with MBC (99.6% purity) at 0, 100, 500, 1,000, 5,000, or 10,000 µg/plate with or without mouse or rat liver S-9 activation (Summers, 1981a). There was a significant, increased reversion rate in TA1537 and TA98 at concentrations equal to, or greater than 5,000 µg/plate with either mouse or rat liver activation. In TA100 (with activation) and TA1537 (without activation) there was a concentration dependent response (less than twice background). The study was acceptable to DPR under TSCA guidelines .

Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 were incubated with MBC (99% purity) at 0, 100, 500, 1,000, 5,000, or 10,000 µg/plate, with or without rat liver S-9 activation (Summers, 1983a). There was no increase in the reversion rate, and there was no cytotoxicity at 10,000 µg/plate. The study was acceptable to DPR under TSCA guidelines .

Salmonella typhimurium strains TA1535, TA97, TA98, and TA100 were incubated with MBC (99% purity) at 0, 100, 500, 1,000, 2,500, or 5,000 µg/plate, with and without rat liver activation (Summers, 1983b). There was no indication of increased reversion rate in two trials. The study was acceptable to DPR under TSCA guidelines .

Salmonella typhimurium strains TA1535, TA97, TA98, and TA100 were incubated with MBC (99% purity) at 0, 100, 500, 1,000, 2,500, 5,000, or 10,000 µg/plate with and without rat liver activation (Summers, 1983c). There no increase in the reversion rate, and no evidence of cytotoxicity at 10,000 µg/plate. The study was acceptable to DPR under TSCA guidelines .

Chinese hamster ovary cells were incubated with MBC (99% purity) at 0 to 628 µM in duplicate cultures (Summers, 1980). There were four trials without rat liver activation and three trials with S-9 activation. There was precipitation at concentrations above 262 µM, which caused toxicity problems. No mutagenicity was detected. The study was acceptable to DPR under TSCA guidelines .

Mouse L5178Y TK+/- cells were incubated with MBC (99% purity) at 0 - 1,000 µg/ml with and without rat liver activation in the first trial (Jotz *et al.*, 1980). Precipitation was seen at 80 µg/ml and above. The second trial was conducted with 0 - 25 µg/ml with activation, and 0 - 100 µg/ml without activation. There was a mutagenic effect (reversion frequencies greater than twice background) at 50 µg/ml without activation, and at 12 µg/ml with activation. The study was acceptable to DPR under TSCA guidelines .

Mouse L5178Y TK+/- cells were incubated with MBC (99% purity) at 0, 25, 50, 100, 150, 200 µM, with and without rat liver activation, in two trials (Summers, 1983d). There was no increase in mutation frequency. The study was acceptable to DPR under TSCA guidelines .

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 were incubated with 5-hydroxy MBC (95% purity) at 0 - 20,000 µg/plate without S-9 rat liver activation and 0 - 16,000 µg/plate with S-9 activation (Russell and Rickard, 1986c). Duplicate plates were used, and five trials with increasing concentration in each. No increase in the reversion rate was reported. The study was acceptable to DPR under TSCA guidelines .

MBC (99% purity) was tested in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, and in *Escherichia coli* WP2 *hcr* to detect gene mutations (Shirasu *et al.*, 1977c). All results were negative. The study was unacceptable to DPR under TSCA guidelines because the dosages were not justified, there were no analyses of dosing solutions, and insufficient individual data for independent analyses.

Chromosomal Aberration- Benomyl

Benomyl (95% purity) was given in a single dose by oral gavage at 0 (0.5% aqueous sodium carboxymethylcellulose), 1250, 2500, or 5000 mg/kg to BDF1 mice (6/sex/dose group) with termination times of 24, 48 and 72 hours (Sasaki, 1990). No mortalities were reported. No effect on the ratio of polychromatic erythrocytes (PCE) to PCE + NCE was noted. An increase in micronuclei formation in PCEs was reported at 24 and 48 hours, with statistical significance ($P < 0.05$) at all three doses. At 72 hours, there was a statistically significant ($P < 0.05$) increase in micronuclei at 2500 and 5000 mg/kg. Also, a statistically significant ($P < 0.05$) trend was noted at 24 and 48 hours. The study was acceptable to DPR under TSCA guidelines .

Technical benomyl (96.1% purity) at 0 (corn oil), 625, 1250, 2500, or 5000 mg/kg was given in a single dose by oral gavage to B6D2F1/Cr-1BR mice (5/sex/dose group) (Stahl, 1990). Positive control mice (5/sex/group) received a single dose of cyclophosphamide. Mice were terminated 24 hours after dosing, and at least 2 slides/animal were prepared. There was no increase in aberrations at the 24 hour harvest time. The study was unacceptable to DPR under TSCA guidelines as there was only a single termination time without justification.

Technical benomyl (98.7% purity) was tested on Chinese hamster lung cells with and without male rat liver activation (Aroclor-induced) (Sasaki, 1988). Cells treated without activation were incubated for 24 or 48 hours, at 2 cultures per concentration, and two trials at 0 (DMSO), 1.416, 2.832, 5.664, 11.33, or 22.66 $\mu\text{g}/\text{ml}$. Cells treated with activation were incubated for 6 hours, washed, and incubated a further 12 or 18 hours, with duplicate cultures, and two trials. In the first trial, the concentrations were 0, 3.119, 6.238, 12.48, 24.95, or 49.9 $\mu\text{g}/\text{ml}$. In the second trial, the concentrations were 0, 5.664, 11.33, 22.66, 45.31, or 90.63 $\mu\text{g}/\text{ml}$. One hundred metaphases per culture were scored for polyploidy and for chromatid/chromosome aberrations. The results were positive for structural and numerical chromosomal aberrations with and without activation. The effect without activation was greater than the effect with activation. The study was acceptable to DPR under TSCA guidelines .

Technical benomyl (99% purity) was incubated with Chinese hamster ovary cells at 0, 9.4, 18.8, 37.5, 75, or 150 $\mu\text{g}/\text{ml}$ for 2 hours with S-9 activation, or at 0, 0.63, 1.25, 2.5, 5 or 10 $\mu\text{g}/\text{ml}$ for 22 hours without activation (Evans and Mitchell, 1980). There was an increase in sister chromatid exchange at all concentrations tested, with or without activation. However, a high background rate confounded interpretation. The study was acceptable to DPR under TSCA guidelines .

Benomyl (purity unstated) at 2 $\mu\text{g}/3 \text{ cm} \times 5 \text{ cm}$ filter paper triangle induced a high frequency of mitotic non-disjunction in *Aspergillus nidulans* in the spot test (Bignami *et al.*, 1977). Benomyl at 4 $\mu\text{g}/\text{ml}$ also promoted non-disjunction in the *Aspergillus* non-selective test. The study was not acceptable to DPR under TSCA guidelines due to limitations in the study design.

Benomyl (purity unknown) and MBC (purity unknown) at 100 µg/ml induced chromosome aberrations in the hyphae of *Botrytis cinerea* and the root tips of the onion, *Allium cepa* (Richmond and Phillips, 1975). The study was unacceptable to DPR under TSCA guidelines due to limitations in the study design.

Chromosomal Aberration- MBC

HeLa cells were exposed to MBC (purity not stated) at 10^{-7} to 10^{-4} M, or 20 µg/ml for various time periods (Everhart, no date). Cell cycle progression was halted in mitosis. Cells entered mitosis, but could not progress to the G1 stage. The study was unacceptable to DPR under TSCA guidelines as it was not applicable for the data requirement due to non-standard design.

MBC (purity unstated) at doses of 100 mg/kg or above was mutagenic in mice in the micronucleus test (Seiler, 1976). Benomyl at 1000 mg/kg was positive in the same test. Doses were given twice and the mice were terminated six hours after the second dosing. The study was unacceptable to DPR under TSCA guidelines due to limitations in the study design.

In order to evaluate chromosome loss or breakage, 1 mg/ml Benlate® (50% benomyl) or 0.5 mg/ml were dissolved in 0.5% DMSO and fed to deprived adult male *D. melanogaster* [yw^+B/B^SYy^+ strain](Lamb and Lilly, 1980). Neither benomyl nor MBC increased the numbers of offspring resulting from paternal chromosome losses, exchanges, or breaks. The human lymphocyte study involved blood samples cultured with MBC for 44 hours. MBC did not increase the numbers of cells with chromosome aberrations, even though the chromosomes incubated with MBC were more contracted than the controls. The study was unacceptable to DPR under TSCA guidelines due to limitations in the study design.

Long Evans rats were used to derive (1) bone marrow cell suspension samples of 21-day pregnant rats for chromosomal aberration analyses, and to derive (2) embryonic tissues for culturing for chromosomal aberration analyses. Tests were conducted with Fundazol 50WP (similar to Benlate®) (Ruzicska *et al.*, 1976). Test material was administered to pregnant female rats by gavage at 25, 50, 200, or 500 mg/kg-day on gestation days 7 through 14 in the first of these studies. In addition, peripheral blood samples from 20 male workers in the manufacturing plant were compared with samples from 15 control workers. Both the bone marrow and worker epidemiological studies were negative. However, in the rat embryonic tissue, the ratio of chromosome aberrations was significantly ($P < 0.05$) increased at 200 and 500 mg/kg-day. The study was unacceptable to DPR under TSCA guidelines due to lack of validation of technique and incomplete reporting.

Other Genotoxic Effects- Benomyl

Seeded rat liver hepatocytes were treated with tritiated thymidine in the presence of benomyl at 0.00005, 0.0005, 0.05, or 0.5 mg/ml (Tong, 1981c). Nuclear grain counts above background [a minimum of 5 counts/nucleus to be positive] were recorded. The results were negative by those criteria. The study was unacceptable to DPR under TSCA guidelines because there was inadequate description of the test article, no analysis of the dosing solution, insufficient individual data, no justification for the wide range of dosages selected, and no QA/GLP.

Benomyl induced genetic segregation (haploidization) in a diploid strain of *Aspergillus nidulans* (Kappas *et al.*, 1974). The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

A *rec* assay was conducted in *Bacillus subtilis* as part of a series of studies on benomyl (Shirasu *et al.*, 1977d). The results were negative. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Other Genotoxic Effects- MBC

B6C3F Mouse hepatocytes were exposed to MBC (purity not given) at 0, 0.0125, 0.125, 1.25 12.5 or 125 µg/ml for 18-20 hours (Tong, 1981a). No effect on DNA repair was reported. The study was acceptable to DPR under TSCA guidelines .

F344 male rat hepatocytes were exposed to MBC (purity not given) at 0, 0.0125, 0.125, 1.25 12.5 or 125 µg/ml for 18-20 hours (Tong, 1981b). The high dose killed the cultures. No effect on unscheduled DNA synthesis was reported. The study was acceptable to DPR under TSCA guidelines .

Bacillus subtilis (M45 and H17) were exposed to MBC (99% purity) without S9 activation at 0, 20, 100, 200, 500, or 1000 µg/10 mm disk in 20 µl (Shirasu *et al.*, 1977b). There was no evidence of differential growth, inhibition, or cytotoxicity. The study was not acceptable to DPR under TSCA guidelines because there was no S9 activation.

A plate test and a liquid test were performed using *Aspergillus nidulans* with benomyl and MBC (Morpurgo *et al.*, 1979). Both compounds were positive for chromosomal non-disjunction. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

Field voles were given MBC (purity unstated) at 250 mg/kg in gum Arabic by gavage in two treatments, 24 hours apart (Tates, 1979). The contents of the seminiferous tubules were examined 1-16 days after treatment. In a second part of the study, voles were given a single intraperitoneal injection of benomyl (purity not stated) at 50, 250, or 500 mg/kg. The contents of the seminiferous tubules were examined 1-14 days after treatment. The frequencies of non-disjunction spermatids or of diploid spermatids were measured. Benomyl did not have an effect, but MBC was effective in inducing non disjunction. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

MBC (99% purity) was tested in the same systems reported for benomyl above by the author (Shirasu *et al.*, 1977c). All results were negative. The study was unacceptable to DPR under TSCA guidelines because of limitations in the study design.

F. REPRODUCTIVE TOXICITY

Summary- No specific reproductive effects of benomyl were observed in female rats; however, male testicular function was adversely affected. The parental female NOEL was 234 mg benomyl/kg-day, based on a decrement in body weight gain. The NOEL for decreased testicular sperm counts, decreased testicular weight, and degeneration and atrophy of seminiferous tubules was 28.2 mg benomyl/kg-day. The pup NOEL was 28.2 mg benomyl/kg-day based on lower birth weight and decrement in body weight gain. Acute exposure to MBC on the afternoon of proestrus caused aneuploidy in hamster oocytes leading to early pregnancy loss.

Dietary- Rat

MBC (50 or 70% active ingredient as a wettable powder) was fed to CD rats at 0, 100, 500, or 5000 ppm of active ingredient, with a fifth group receiving 2500 ppm increased to 10,000 ppm after 20 weeks (Haskell, 1972). The F₀ rats were "borrowed" from a combined chronic toxicity/oncogenicity study. The NOEL was 500 ppm MBC, based on neonatal growth reduction at dosages of 2500 ppm and above. The study was not acceptable to DPR under FIFRA guidelines because of inadequate study design, absence of feed analysis, and the lack of a Maximum Tolerated Dose (MTD). The results were considered supplemental.

In a three-generation reproduction study in rats, no adverse effects were reported at dosages ranging from 100 to 2500 ppm benomyl (Sherman, 1968b). The study was not acceptable to DPR under FIFRA guidelines because of inadequate group size and lack of feed analysis despite demonstrable instability of the test article. This is apparently the study that USEPA used to set their RfD (0.05 mg/kg-day), using a decrease in weanling weight at 500 ppm (but not at 2500 ppm) to arrive at a NOEL of 100 ppm (5 mg/kg-day) (USEPA, 1997a).

Crl:CD BR rats (30/sex/group) were fed on a diet containing benomyl (99% purity) at 0, 100, 500, 3,000, or 10,000 ppm for three generations (Mebus, 1991). Based on consumption data, the mean daily intake of benomyl was 0, 5.7, 28.2, 168, and 553 mg/kg-day for P₁ males, and 0, 7.1, 34.7, 210, and 712 mg/kg-day for P₁ females; 0, 7.8, 38.6, 234, and 954 for F₁ males, and 0, 9.4, 46.8, 280, and 1168 mg/kg-day for F₁ females. Males dosed at 3,000 and 10,000 ppm exhibited testicular atrophy and degeneration, and lower testicular sperm counts in both the P₁ generation (4/30 and 29/30, respectively) and the F₁ generation (9/30 and 21/25, respectively; Table 8). Oligospermia was noted in the epididymides, both unilateral and bilateral in male rats treated with 3,000 and 10,000 ppm in the P₁ generation (1/30 and 26/30, respectively) and the F₁ generation (9/30 and 20/25, respectively). The NOEL for decreased testicular sperm counts, decreased testicular weight, and degeneration and atrophy of seminiferous tubules was 28.2 mg/kg-day. No reproductive effects were observed in female rats. The parental female NOEL was 234 mg/kg-day, based on decrement in body weight gain (57% of control values). The pup NOEL was 500 ppm based on significantly (P<0.05) lower day 21 pup body weights at 3,000 and 10,000 ppm in both males (8% and 51%, respectively) and females (7% and 52%, respectively) compared to controls. The study was acceptable to DPR under FIFRA guidelines.

Table 8 - The effect of dietary exposure to benomyl on male reproductive parameters in the CD rat (Mebus, 1991).

Parameter	Oral Dosage				
	0 ppm	100 ppm	500 ppm	3,000 ppm	10,000 ppm
Mean Testicular Wt. (g)					
P ₁	1.7	1.7	1.7	1.7	1.4*
F ₁	1.9	1.9	2.0	1.8	1.1*
Testicular Sperm (10 ⁻⁶)					
P ₁	123	134	109	97	63*
F ₁	139	135	136	97*	41*
Testicular Atrophy					
P ₁	2/15 (13%)	1/15 (7%)	1/15 (7%)	2/15 (13%)	15/15+ (100%)
F ₁	0/15 (0%)	0/15 (0%)	1/15 (7%)	1/15 (7%)	12/15+ (80%)
Epididymal Oligospermia					
P ₁	1/30 (3%)	1/30 (3%)	0/30 (0%)	1/30 (3%)	26/30+ (87%)
F ₁	1/30 (3%)	0/30 (0%)	0/30 (0%)	9/30+ (30%)	20/25+ (80%)

- * Significantly different (P<0.05) from control value by Dunnett's Test.
- + Significantly different (P<0.05) from control value by Fisher's Exact Test.

Adult male Wistar rats (27/group) were fed on a diet containing benomyl (50% purity) at 0, 1.0, 6.3, or 203 ppm for 70 days, followed by a 70 day recovery for part of the group (Barnes *et al.*, 1983). Male rats were mated with untreated female rats to determine any changes in male reproductive behavior, ejaculated sperm counts, and fertility index. Male copulatory behavior was not affected by benomyl treatment. No significant alteration in the plasma levels of testosterone, LH or FSH were noted during the exposure phase. Ejaculated sperm counts were significantly (P<0.05) depressed (60% reduction) during the exposure period in animals at 203 ppm compared to controls. After the 70 day recovery period, there was no difference in sperm counts in any group. Benomyl caused significant (P<0.05), dose-related reduction in testes weights (ranging from 11-16%) during the exposure period, which disappeared after the recovery phase. The male fertility index (ratio of pregnant female rats to total number of female rats mated with each treated male) was significantly (P<0.05) reduced (ranging from 19-29%) in treated males compared to controls. After the recovery period, there was no difference in the fertility indices. The data were summary form, and considered supplementary.

Gavage- Rat

Male Wistar rats (proven breeders) were gavaged daily with benomyl (97.5% purity) at 0, 1, 5, 15, or 45 mg/kg-day for 62 days, then bred with untreated females [5 females/male] (Linder *et al.*, 1988). On days 76 to 79 (after continued dosing), the males were terminated. No adverse effects of benomyl on male reproductive performance were noted. At the high dose, statistically significant ($P < 0.05$) effects were noted on testis weight (11% reduction), epididymal weight (15% reduction), reduced cauda sperm (43%), increased sperm abnormalities (4%), and increased sloughing of the germinal epithelium in the seminiferous tubules. The 76-day NOEL for these effects was 15 mg/kg-day. The data were considered supplemental.

Male Sprague-Dawley rats (6/time period) were dosed orally with 100 mg/kg MBC in corn oil and terminated 7.5, 9.5, 10, or 10.5 days post treatment (Nakai *et al.*, 1997). Spermatid nuclear abnormalities were observed in Stage IX-XI on day 9.5 and later. Discontinuous, multiple granular, and fragmentary acrosomes in Stages VII-XI were noted on day 7.5 and later. Poorly formed and absent ectoplasmic specializations were seen in the cytoplasm of Sertoli cells next to acrosome-deficient spermatids. A major abnormality of the manchette was irregular positioning of the manchette microtubules in steps 9-11 spermatids on day 9.5 and later. The data were considered supplemental.

Gavage- Hamster

Female Syrian hamsters (10/group), reproductively synchronized by light-dark cycles, were dosed with 0 or 1,000 mg/kg MBC (95% purity) on the afternoon of proestrus (to coincide with meiotic maturation of the oocytes) and either terminated shortly after ovulation (day 1) to recover oocytes, or bred and killed on gestation days 1-5 of pregnancy to assess fertilization and pre-implantation embryo development and enumerate early implantation sites (Jeffay *et al.*, 1996). MBC induced an increase in aneuploidy (37% vs. 14% in controls) in unfertilized oocytes. There was no effect on the number of oocytes recovered or fertilized. However, MBC increased the proportion of embryos that failed to reach the 8 cell stage on the afternoon of gestation day 3, the morula stage by the morning of gestation day 4, and the blastocyst stage by the afternoon of gestation day 4. The mean number of implantation sites was significantly ($P < 0.05$) lowered in treated females on the afternoon of gestation day 4 (1.6 compared to 8.1 in controls) and the morning of gestation day 5 (6.9 compared to 14.4 in controls). The data were considered supplemental.

Intraperitoneal- Rat

Equivalent molar concentrations of benomyl and MBC were administered to rats intraperitoneally (859 $\mu\text{mol/kg}$) or by direct injection into the testis (1.37 $\mu\text{mol/testis}$) (Lim and Miller, 1997). Testicular levels of benomyl and MBC were measured at various times after both routes of administration. No significant testicular damage was observed until 2 hours after benomyl administration by the intraperitoneal route (Table 9). Intraperitoneal administration of MBC resulted in sloughing of the germinal epithelium of the seminiferous tubules at 1 hour, and increased in severity by 2 hours. The area under the curve from the concentration of MBC in a testis vs. time plot showed a good correlation to the number of tubules which exhibited sloughing. The benomyl area under the curve also exhibited a linear relationship to the severity of the lesion. However, when the contribution of MBC to the response to benomyl was subtracted, no effect of benomyl was discernible. The IC_{50} for testicular microtubule assembly was 5 μM for MBC and 75 μM for benomyl. The effect of benomyl on tubule assembly

appeared to be due to the presence of MBC as a metabolite. The authors concluded that MBC, rather than benomyl was responsible for testicular toxicity and the inhibition of testicular microtubule assembly.

In the second part of the study, intraperitoneal administration of MBC (97% purity) at 262 µg/testis in Sprague-Dawley rats caused little testicular damage in prepubertal animals compared to adults. Differences in the sensitivity to MBC-induced testicular toxicity were not ascribed to differences in the ability to inhibit microtubule assembly. No difference was found in the inhibitory effect of MBC on assembly of prepubertal or adult rat tubulin *in vitro*. The histopathology of juvenile testes injected with MBC was very different from that of similarly treated adult testes. The authors concluded that difference in the composition of testicular cells between the two age groups was responsible for the differences in the effect of MBC on the testes. They surmised that the lack of sloughing of the germ cell epithelium of young animals in response to dosing with MBC was due to the lack of late-stage spermatids, which were sloughed in the testes of adults. Although the reported research was not a FIFRA guideline study, the data aid in understanding benomyl toxicity.

Table 9 - Histological appearance of rat testes following intraperitoneal (859 µmol/kg) and intratesticular (1.37 µmol/testis) administration of benomyl and MBC (Lim and Miller, 1997).

	IP Administration				
	Control	Benomyl 1 hr	Benomyl 2 hr	MBC 1 hr	MBC 2 hr
Normal	92±1.0 ^a	74.2±2.5*	38.7±4.4*	28.6±3.6*	3.2±1.4*
Vacuolization	6.8±1.0	21.6±2.5	33.5±2.2*	51.2±5.0*	47.4±7.8*
Detachment	0.5±0.5	13.3±5.6	48.6±2.9*	38.1±5.4*	85.9±5.0*
Sloughing	0±0	0.7±0.7	2.7±2.1*	6.2±3.5*	37.4±9.8*
Intratesticular Administration					
Normal	85.3±0.6	63.8±4.2*	48.3±1.4*	34.6±1.1*	12.6±2.0*
Vacuolization	13.4±0.5	27.1±4.2*	32.2±2.3*	30.5±1.9*	27.2±1.1*
Detachment	3.1±0.7	8.7±2.0	25.1±1.1*	28.8±4.7*	42.1±3.5*
Sloughing	0.9±0.2	8.7±1.2*	18.0±1.9*	37.2±3.6*	53.3±5.6*

* Significantly different (P<0.05) from control by Scheffe's F test.

a/ Percent incidence ± SD

G. DEVELOPMENTAL TOXICITY

Summary- Benomyl and/or MBC were teratogenic in rats, rabbits, and mice. In the absence of maternal toxicity, benomyl caused enlarged lateral ventricles, enlarged renal pelves, delayed ossification, hydrocephaly, microphthalmia and anophthalmia, fused ribs, fused vertebrae, and decreased ossification in the tail in rats with a NOEL of 30 mg/kg-day. In rabbits, the NOEL for maternal toxicity (weight loss) and terata (fused and/or split ribs and asymmetric vertebrae) was 20 mg MBC/kg-day. The rabbit NOEL for developmental toxicity (post-implantation loss) was 10 mg MBC/kg-day. In mice, the NOEL for developmental effects (increased incidence of supernumerary ribs, enlarged renal pelves, cleft palate, hydronephrosis, fused ribs, fused vertebrae, short and/or kinky tail, and delayed ossification in vertebral centra) was 50 mg benomyl/kg-day.

Gavage- Rat

Benomyl (99.2% purity) at 0, 3, 10, 30, 62.5 or 125 mg/kg-day was administered by gavage to CD rats on days 7 through 14 of gestation (Staples, 1980). The NOEL for maternal toxicity was 125 mg/kg-day, as all females survived the treatment without decrement in weight gain, or exhibiting clinical signs. There was a significant ($P < 0.05$) decrement in fetal weights (10 and 17%, respectively) at the two top doses. Eye malformations, ranging from slight microphthalmia to frank anophthalmia were also observed in these groups (8/20 litters at 125 mg/kg-day; 4/23 litters at 62.5 mg/kg-day). In the 125 mg/kg-day group, 15/21 fetuses with microphthalmia were affected bilaterally, and 5/10 with microphthalmia in the 62.5 mg/kg-day group were affected bilaterally. Histologic examination of affected eyes revealed several pathologic abnormalities. These consisted of "... very small or irregular lenses, or rarefaction of lens material; debris in the lens, vitreous chamber, or at the optic disc; possible retro-bulbar glandular adnexa; disrupted, distorted, or compressed retinal layers; bulging of the choroid in the area of the ciliary process; thickened nerve fiber layer." The developmental NOEL was 30 mg/kg-day for eye malformations. The study was acceptable to DPR under FIFRA guidelines when taken in conjunction with the following study.

Benomyl (99.1% purity) at 0, 3, 10, 30, or 62.5 mg/kg-day was administered by gavage to CD rats on days 7 through 14 of gestation (Staples, 1982). Decreased fetal weights (5%), microphthalmia (in 2/16 litters) and hydrocephaly (1/16 litters) were observed only at the high dose. The NOEL for developmental toxicity was 30 mg/kg-day. The study was acceptable to DPR under FIFRA guidelines (even though only fetal heads were examined in order to clarify craniofacial malformations noted in the former study) when taken in conjunction with the preceding study (Staples, 1980).

Pregnant Wistar rats (20, 19, 25, 25 and 11 for the respective doses) were dosed with benomyl (purity unstated) by gavage at 0, 15.6, 31.2, 62.5, or 125 mg/kg-day on days seven through sixteen of gestation (Kavlock *et al.*, 1982). No compound-related maternal toxicity was reported. At 125 mg/kg, 6 of 11 pregnant dams had full litter resorptions. Fetuses in the top two dose groups (125 and 62.5 mg/kg-day) exhibited enlarged lateral ventricles, enlarged renal pelves, delayed ossification, hydrocephaly, microphthalmia, fused ribs, fused vertebrae, and decreased ossification in the tail. There was a dose-related reduction in fetal weight. The NOEL for developmental toxicity was 31.2 mg/kg-day. The published study was in summary form, and thus, unacceptable to DPR under FIFRA guidelines. The information was considered supplemental.

Sprague-Dawley rats (a total of 13 dams divided between three dosages) were dosed orally with MBC (purity unstated) at 9.6, 19 and 38 mg/kg-day, or benomyl at 116 mg/kg-day on days 8 to 15 of gestation (Delatour and Richard, 1976). Benomyl was not reported to have caused defects at that dosage. MBC at 9.6 mg/kg-day caused no developmental defects. At 19 mg/kg-day, MBC caused 72% embryo lethality and 100% "external anomalies" among the survivors, and 100% embryo lethality at 38 mg/kg-day. The anomalies were not quantified; however, exencephaly was noted as "common" for MBC. The study was unacceptable to DPR under FIFRA guidelines due to the limitations of the study design.

Female Holzman rats were dosed by gavage with MBC (95% purity) at 0, 25, 50, 100, 200, 400, or 1000 mg/kg-day on days 1 through 8 of pregnancy and killed on day 9 (Cummings *et al.*, 1990). There was a trend in increased resorptions from controls (10%) to rats treated with 400 mg/kg-day (27%), but the differences were not statistically significant. The data indicated that dosages of MBC up to 400 mg/kg-day did not produce pregnancy failure, adverse maternal effects (other than partial decidual growth inhibition), or clear evidence of embryotoxicity when administered during very early pregnancy. The information was considered supplemental by DPR.

Female Holzman rats were dosed by gavage with MBC (95% purity) at 0, 100, 200, 400, or 600 mg/kg-day on days 1 through 8 of pregnancy and killed on days 11 or 20 (Cummings *et al.*, 1992). A significant ($P<0.05$) number of dams at all dosages exhibited complete resorption at 20 days (Table 10). The percentage of viable fetuses in the surviving litters was significantly ($P<0.05$) less than controls at all dosages. At all dosages, the number of live fetuses exhibiting delayed ossification was significantly ($P<0.05$) greater than controls. In a separate experiment, dams dosed with 600 mg/kg-day on days 1-3 (N=5) exhibited the same number of live (11.8 ± 0.8) and resorbed (0) fetuses per litter as the controls (N=6; 11.2 ± 1.1 and 0.5 ± 0.5 , respectively). However, dams dosed with 600 mg/kg-day on days 4-8 (N=6) had significantly ($P<0.01$) less live fetuses per litter (2.8 ± 2.1) and greater numbers of resorbed fetuses (9.0 ± 2.6). The published study was in summary form, and considered supplemental by DPR.

Table 10- Effect of MBC on the pregnancy outcome in rats when administered on days 1 through 8 of pregnancy (Cummings *et al.*, 1992).

Parameter	Dose of MBC (mg/kg-day)				
	0	100	200	400	600
Pregnant dams (#)	10	11	11	11	10
Complete Resorption (#)	0	4*	7*	9*	6*
Terminal BW (g)	330 ± 7	$299\pm 11^*$	$279\pm 10^*$	$259\pm 7^*$	$273\pm 8^*$
Viable fetuses per litter (%)	89	35*	26*	7*	15*
Live Fetus Wt (g)	3.9 ± 0.1	$2.8\pm 0.2^*$	$3.1\pm 0.1^*$	$2.8\pm 0.4^*$	$2.9\pm 0.2^*$

* Significantly ($P<0.05$) different from vehicle-treated controls using a *t* test.

Female Wistar rats (20/dose) were given MBC (98% purity) at 0, 20, 40, or 80 mg/kg-day in aqueous gum acacia (4%) by gavage on days 6 through 15 of gestation (Janardhan *et al.*, 1984). The number of dead and resorbed fetuses was significantly ($P<0.01$) increased (73% and 64%, respectively), compared to controls (29%), at 40 and 80 mg/kg-day. Even at 20 mg/kg-day the number of dead and resorbed fetuses was elevated (48%), though not significantly. There was no NOEL for embryotoxicity. No gross or visceral abnormalities were reported, nor any skeletal malformations. The data were considered supplemental.

Pregnant Sprague-Dawley rats (6-8/treatment group) were dosed by oral gavage with 0 or 31.2 mg/kg-day benomyl (purity not stated) on days 7-16 or days 7-21 of gestation while on a diet containing either 24% or 8% casein (Zeman *et al.*, 1986). No fetal skeletal effects were seen in any dose group. On a per fetus basis, there was an increased number of brain abnormalities in treated rats. The increase was more pronounced in rats fed on a normal diet and dosed until gestation day 21, than in any of the other dose groups. There was no information on the per litter incidence of fetal anomalies. The data, from a published study, were considered supplemental.

Pregnant Sprague-Dawley rats, fed on either a normal diet (24% casein) or one containing 8% casein, were dosed with benomyl (62.4 mg/kg-day) by oral gavage on days 7 through 21 of gestation (Hoogenboom *et al.*, 1987). Ocular anomalies, including retinal dysplasia, cataracts, microphthalmia, and anophthalmia, occurred in 43.3% of the fetuses from dams on a normal diet. Protein deprived animals exhibited a greater frequency of anomalies (62.5%) than fetuses from animals on a normal diet. The data, from a published study, were considered supplemental.

Pregnant Sprague-Dawley rats, fed normally or on an 8% casein diet, were dosed by oral gavage with benomyl at 31.2, 62.5, or 125 mg/kg-day on days 7-21 of gestation (Ellis *et al.*, 1987). Malformations increased in incidence and severity with increasing benomyl dosage. The frequency of these effects nearly doubled at each dose in animals on protein-deficient diets. Protein deficiency alone produced only decreased fetal weight. The most common systemic malformations included cleft palate, micromelia, hydroureter, and misshapen tails. No fetus was entirely normal at the highest benomyl dose. The data, from a published study, were considered supplemental.

Pregnant Sprague-Dawley rats were dosed with benomyl (62.5 mg/kg/day) by oral gavage on days 7-20 of gestation (Ellis *et al.*, 1988). Hydrocephalus occurred in 65.2% of the fetuses examined on gestational day 16, and in 58.6% on gestational day 20. However, the incidence more severe in the gestational day 20 fetuses. A second common anomaly, termed periventricular overgrowth (PVO), consisted of sub-ependymal cell masses that obliterated normal subcortical structures. PVO occurred in 34.8% of the fetuses examined on gestation day 16, and 76.5% on gestational day 20. PVO distorted the cerebral aqueduct in a large number of the fetuses with ventriculomegaly, and moderate and severe ventriculomegaly was associated with a narrow or completely occluded cerebral aqueduct on gestation day 20. The data, from a published study, were considered supplemental.

Diet- Rats

Charles River CD rats (27 to 28 per dose group) were exposed to a formulation containing MBC (53% active ingredient/mg) at 0, 100, 500, 2,500, 5,000, 7,500 or 10,000 mg formulation/kg-day on days 6 through 16 of gestation (Culik *et al.*, 1970). There was no indication of maternal or fetal toxicity. The study was unacceptable to DPR under FIFRA guidelines because the dose levels were inadequate; there was no feed analysis, no maternal toxicity, and no indication of the effects of the formulation excipients on the absorption of the active ingredient.

Gavage- Rabbit

New Zealand White Rabbits (20/dose) were dosed with MBC (98.7% purity) at 0, 10, 20, or 125 mg/kg-day once daily by gavage on gestation days 7 through 19 (Feussner, 1985). At 125 mg/kg-day, maternal toxicity was expressed as weight loss (-3%). Two high dose does aborted (days 22 and 25), but no abortions occurred in other dose groups. One doe at 20 mg/kg-day and four at 125 mg/kg-day, having red exudate in the cage pan on several days, were found to have totally resorbed all concepti. Three other high dose does resorbed all concepti, despite the absence of clinical findings. Excluding litters with totally resorbed concepti, the mean litter size was reduced 15, 24, and 28% compared to controls for animals dosed with 10, 20, and 125 mg/kg-day, respectively. The reduced litter size was due to increased post-implantation loss (Table 11) and reduced ovulation (which was not chemically related). The number of litters with at least one resorption from animals dosed with 10 mg/kg-day was not significantly different from that of controls. Although the incidence of post-implantation loss was significantly greater at 10 mg/kg-day (13.5%) than in controls (2.8%), this effect was due to a single animal with 9 resorptions. However, the best estimate of biological effects is obtained using the litter as the unit for comparison, as it is the mother who is dosed (USEPA, 1991). Consequently, the NOEL for post-implantation loss was 10 mg/kg-day. Malformations, at the high dose, consisted mainly of fused and/or split ribs and asymmetric vertebrae. The NOEL for maternal toxicity (weight loss) and malformations (fused and/or split ribs and asymmetric vertebrae) was 20 mg/kg-day. The study was acceptable to DPR under FIFRA guidelines.

Table 11- Effect of MBC on post-implantation loss and fetal malformations in rabbits when administered on days 1 through 12 of pregnancy (Feussner, 1985).

Parameters	Dose level (mg/kg-day)			
	0	10	20	125
Post-implantation loss - resorption sites/implantation sites	3/108 (2.8%)	16/119** (13.5%)	11/102* (10.8%)	46/95** (48.4%)
No. animals with total litter resorption	0	0	1	7
Fraction of c-sectioned animals with post-implantation loss	3/14 (21%)	4/16 (25%)	6/17* (35%)	12/16** (75%)
Fraction of litters with fetal malformations	9/14 (64%)	7/16 (44%)	5/16 (31%)	8/9* (89%)
Fraction of fetuses with malformations	11/105 (11%)	12/103 (12%)	6/91 (7%)	24/49** (49%)

* Significantly different (P<0.05) from control by Fisher's exact test.

** Significantly different (P<0.01) from control by Fisher's exact test.

New Zealand White rabbits (4/dose) were given MBC (98% purity) at 0, 40, 80, or 160 mg/kg-day in aqueous gum acacia (4%) by gavage on days 6 through 18 of gestation (Janardhan *et al.*, 1984). There was a dose related decrease in the percentage of viable fetuses in treated animals (17/20 at 40 mg/kg-day, 18/23 at 80 mg/kg-day, and 10/15 at 160 mg/kg-day) compared to controls (17/17). There was no NOEL for embryotoxicity. No gross

or visceral abnormalities were reported, nor any skeletal malformations. The data were considered supplemental.

New Zealand White rabbits (20/dose) were dosed by gavage with benomyl (97.4% purity) at 0, 15, 30, 90, or 180 mg/kg-day on days 7-28 of gestation (Munley, 1995). At the high dose, maternal toxicity was manifested as reduced food consumption during the first and last weeks of dosing, and an increase in clinical signs (anal staining). Developmental toxicity at 180 mg/kg-day was manifested as a significant ($P < 0.05$) increase in the incidence (one each in two litters) of small renal papillae compared to controls (none). The maternal and developmental NOELs were 90 mg/kg-day. The study was acceptable to DPR under FIFRA guideline requirements.

Diet- Rabbit

New Zealand White Rabbits (12, 13, and 9 for the respective doses) were fed a diet containing a benomyl formulation (Fungicide 1991; 50% benomyl) at 0, 100, or 500 ppm on days 8 through 16 of gestation (Busey, 1968). There was no reported indication of developmental or maternal toxicity. The study was unacceptable to DPR under FIFRA guidelines because of the lack of food analysis, inadequate group size, insufficient skeletal exams, and the maximum tolerated dose was not reached.

Diet- Mouse

CD-1 mice (25, 25, 20, and 25/dose, respectively) received benomyl (purity unstated) at 0, 50, 100, or 200 mg/kg-day by gavage on days 6 through 16 of gestation (Kavlock *et al.*, 1982). Fetal mortality was significantly ($P < 0.05$) increased at 200 mg/kg-day (22% compared to controls, 9%). The NOEL for developmental effects (increased incidence of supernumerary ribs, enlarged renal pelves, cleft palate, hydronephrosis, fused ribs, fused vertebrae, short and/or kinky tail, and delayed ossification in vertebral centra) was 50 mg/kg-day. The published study was in summary form, and thus, unacceptable to DPR under FIFRA guidelines, but the information was considered supplemental.

Special study

Data derived from four developmental toxicity studies (2 rat studies, 1 rabbit, and 1 hamster study) submitted to the WHO were used as the basis for calculating benchmark doses (BDs) for 19 developmental endpoints (Mantovani *et al.*, 1998). The data were evaluated on a per implant/fetus basis, rather than on a per litter basis which is considered more toxicologically relevant (USEPA, 1991). BDs were derived from response rate increases of 1, 5, and 10%. The values were compared to the lowest observed adverse effect levels (LOAELs) and no-observed adverse effect levels (NOAELs) obtained by Fisher's exact test on a per implant/fetus basis. Frank effects observed only at the top dose and/or small sample size tended to increase the 95% confidence limits and this influenced the determination of the benchmark dose. Generally, the benchmark dose approach provided slightly more conservative estimates of toxicity than the NOAEL. The benchmark doses at the 1 or 5% response rate were similar to the NOAELs, or even lower for several parameters. The LOAEL in most instances was similar to the benchmark dose at the 10% response rate. Reference doses were obtained by dividing the BD01 by an uncertainty factor of 10 or 100. For two critical parameters (hydrocephalus in a rat study, and resorption rate in the rabbit study), a NOAEL could not be identified, but a benchmark dose was easily calculated. This published study was considered supplemental information.

H. NEUROTOXICITY

Summary- Neither benomyl nor its metabolite, MBC, caused any histopathological changes indicative of delayed neurotoxicity in the chicken. The NOEL for clinical signs (ataxia, low carriage, wing droop) in the chicken was 2,500 mg benomyl/kg. The NOEL for clinical signs (liquid stools, urine-stained fur) in the rat was 500 mg benomyl/kg. There was no indication, behaviorally or histopathologically, of delayed neurotoxicity in the rat.

Oral- Rat

Sprague-Dawley Crl:CD®BR VAF/Plus® rats (10/sex/dose) received benomyl (97.4% purity) at 0, 500, 1000 or 2000 mg/kg by oral gavage (Foss, 1993). Both male (6/10) and female (1/10) rats at 2000 mg/kg, and male rats (3/10) at 1000 mg/kg exhibited soft or liquid feces. Between days 1 and 3, one female and two male rats at 2000 mg/kg, and one female rat at 1000 mg/kg had urine-stained fur. The number of movements and the time spent in movement was reduced in females at 2000 mg/kg, compared to controls. The NOEL for clinical signs for a single dose was 500 mg/kg. Statistically significant ($P < 0.01$) decrements in body weight gain were seen in males at 1000 mg/kg (-2.0 g) and 2000 mg/kg (-5.3 g). The decrement in body weight gain was accompanied by a significant ($P < 0.01$) decrement in food consumption (33% at each dosage). There was no indication of delayed neurotoxicity. The study was acceptable as supplementary data.

Oral- Hens

Benomyl (purity not given) was administered at 0, 500, 2500, or 5000 mg/kg by oral gavage to hens, with TOCP at 750 mg/kg as a positive control (Geil *et al.*, 1978a). The results were equivocal because there was an underlying disease in the hens, which compromised the data. The study was unacceptable to DPR.

Benomyl (purity not given) was administered at 0, 500, 2500, or 5000 mg/kg by oral gavage to hens, with TOCP at 1200 mg/kg as a positive control (Jessup, 1979). The NOEL for death and clinical signs (ataxia, low carriage, wing droop) was 2500 mg/kg. There was no histological evidence of delayed neurotoxicity. The data were considered supplemental.

MBC (purity not given) was administered at 0, 500, 2500, or 5000 mg/kg by oral gavage to hens, with TOCP at 750 mg/kg as a positive control (Geil *et al.*, 1978b). There were clinical signs of neurotoxicity (ataxia, low carriage, and wing droop) at 5000 mg/kg, with a NOEL of 2500 mg/kg. No histological indication of delayed neurotoxicity from MBC was reported. The data were considered supplemental.

RISK ASSESSMENT

A. HAZARD IDENTIFICATION

Benomyl entered the risk assessment process because of its teratogenicity, oncogenicity, reproductive toxicity, and adverse effects on the liver caused by repetitive dosing. A summary of the toxic effects of benomyl and its principal metabolite, MBC, as presented in this document, is contained in Table 12.

Table 12 - Summary of selected benomyl (B) and methyl 2-benzimidazolecarbamate (MBC) toxicology studies.

STUDY	SPECIES	EFFECT	LOEL	NOEL	GENOTOXIC	REF ^a
			(mg/kg-day ^b)			
acute (1d)	rat	male repro. (B)	50	25		1
neurotox. (1d)	rat	clinical signs	1000	500		2
subchronic (7d)	rat	hepatotoxicity (B)	40	-		3
subchronic (85d)	rat	fertility (MBC)	200	100		4
chronic (2 yr)	dog	hepatotoxicity (MBC)	13.5	2.6		5
chronic (2 yr)	dog	hepatotoxicity (B)	75	15		6*
chronic (2 yr)	rat	hepatotoxicity (MBC)	25	4.9		7
chronic (2 yr)	mouse	male repro. (MBC)	225	75		8*
chronic (2 yr)	mouse	hepatotoxicity (MBC)	45	23		9
repro.	rat	male repro. (B)	168	28		10*
develop.	rat	terata (B)	62.5	30		11*
develop	rat	terata (B)	62.5	31.2		12
develop.	rabbit	develop. toxicity (MBC)	20	10		13*
develop.	mouse	terata (B)	100	50		12
mutagenicity	bacteria	<i>in vitro</i> (MBC)			+	14,15*
mutagenicity	bacteria	<i>in vitro</i> (B)			-	16-20*
mutagenicity	CHO	<i>in vitro</i> (MBC)			-	21*
mutagenicity	CHO	<i>in vitro</i> (MBC)			+	22*
mutagenicity	m. lymph	<i>in vitro</i> (MBC)			-	23*
micronucleus.	mouse	<i>in vivo</i> (B)			+	24*
chrom. abber.	CH lung	<i>in vitro</i> (B)			+	25*
SCE	CHO	<i>in vivo</i> (B)			+	26*
unsched. DNA syn.	mouse	<i>in vitro</i> (MBC)			-	27*
unsched. DNA syn.	rat	<i>in vitro</i> (MBC)			-	28*

a/ 1. Hess *et al.*, 1991; 2. Foss, 1993; 3. Igbedioh and Akinyele, 1992; 4. Goldman *et al.*, 1989; 5. Sherman, 1972a; 6. Sherman, 1970; 7. Sherman, 1972b; 8. Wood, 1982; 9. Donaubaauer, 1982; 10. Mebus, 1991; 11. Staples, 1982; 12. Kavlock *et al.*, 1982; 13. Feussner, 1985; 14. Russell and Rickard, 1986c; 15. Summers, 1981a; 16. Summers, 1981b; 17. Russell and Rickard, 1986a; 18. Russell and Rickard, 1986b; 19. Summers, 1983a,b,c; 20. Russell and Rickard, 1986c; 21. Summers, 1980; 22. Jotz *et al.*, 1980; 23. Summers, 1983d; 24. Sasaki, 1990; 25. Sasaki, 1988; 26. Evans and Mitchell, 1980; 27. Tong, 1981a; 28. Tong, 1981b.

b/ Test doses were not converted to benomyl equivalents (see text).

* Study acceptable to DPR under TSCA or FIFRA guideline requirements.

As pharmacokinetic data show a rapid conversion of benomyl to MBC, toxicity data on MBC are considered applicable to benomyl. However, an appropriate adjustment for the difference in their molecular weights (a milligram of MBC is equivalent to 1.52 mg benomyl) needs to be made. MBC (also known as carbendazim) is a fungicide of equivalent effectiveness and range to benomyl, and is the principal product of toxicological concern. In the MBC studies, the administered dosages of MBC need to be adjusted (multiplied by 1.5) to approximate absorbed benomyl equivalents.

Acute Toxicity

Most occupational exposures to benomyl involve dermal absorption (Haskell and Mehler, 1999). Therefore, a short-term dermal NOEL derived from an acute dermal toxicity study would be the most appropriate NOEL for assessing the risks of potential acute occupational exposures to benomyl. Unfortunately, no such single-dose dermal toxicity studies were available in the DPR data base, or from a search of the open literature. Consequently, short-term oral toxicity studies were examined to obtain the basis for calculating margins of exposure associated with acute exposure to benomyl.

Only two, single oral dose studies (non LD₅₀ studies) were available from the toxicological database. A single dose, acute neurotoxicity study involving laboratory rats indicated a NOEL of 500 mg benomyl/kg for clinical signs (liquid stools and urine stained fur). However, clinical signs are not one of the toxicological endpoints of greatest importance for benomyl. Hepatotoxicity, reproductive toxicity, and developmental toxicity, detected in multiple laboratory species are of greater concern with short term exposures. No studies on the hepatotoxicity of a single dose of benomyl were available in the DPR data base or published literature.

The second single oral dose study examined the toxic effects of benomyl on the male reproductive system in rats (Hess *et al.*, 1991). The NOEL for sloughing of the germinal epithelium in the seminiferous tubules was 25 mg benomyl/kg. However, this was not the lowest NOEL for an acute toxicological endpoint of concern.

Developmental toxicity may be manifested as the result of a single dose (Schardein, 1985; Ogata *et al.*, 1984; USEPA, 1991). Consequently, it was assumed, in the absence of data to the contrary, that the observed effects in developmental toxicity studies were elicited from a single dose. Benomyl and/or MBC were teratogenic in mice, rats, and rabbits. In mice, the NOEL for developmental effects (increased incidence of supernumerary ribs, enlarged renal pelves, cleft palate, hydronephrosis, fused ribs, fused vertebrae, short and/or kinky tail, and delayed ossification in vertebral centra) was 50 mg benomyl/kg-day (Kavlock *et al.*, 1982). In rats, benomyl caused enlarged lateral ventricles, enlarged renal pelves, delayed ossification, hydrocephaly, microphthalmia and anophthalmia, fused ribs, fused vertebrae, and decreased ossification in the tail with a NOEL of 30 mg benomyl/kg-day (Staples, 1980; Kavlock *et al.*, 1982; Staples, 1982). In the rabbit, the primary metabolite of benomyl, MBC, caused fused and/or split ribs and asymmetric vertebrae, with a NOEL of 20 mg MBC/kg-day (Feussner, 1985).

Post-implantation loss, another type of developmental toxicity, was also caused by benomyl and/or MBC in both rats (Staples, 1980; Kavlock *et al.*, 1982; Janardhan *et al.*, 1984; Cummings *et al.*, 1990, 1992;) and rabbits (Janardhan *et al.*, 1984; Feussner, 1985). The lowest range of doses tested was in a rabbit developmental toxicity study (Feussner, 1985). The NOEL for post-implantation loss caused by MBC was 10 mg MBC/kg-day. The NOEL, 10

mg MBC/kg-day, was converted to an equivalent amount of benomyl absorbed per kg by multiplying with the adjustment factor [1.5] explained above. The NOEL, in benomyl equivalents, is therefore 15 mg benomyl equivalents/kg [10 mg MBC/kg x 1.5] for a bolus oral dose. This critical NOEL of 15 mg benomyl equivalents/kg for post-implantation loss in rabbits was used as the basis for estimating acute margins of exposure from potential exposures to benomyl.

Chronic Toxicity

The principal non-oncogenic effect from long-term, repetitive dosing with benomyl and/or MBC was hepatotoxicity, which was observed in mice, rats and dogs. Mice appeared to be the least sensitive laboratory animal to hepatotoxicity, exhibiting centrilobular hypertrophy, single cell necrosis, increased pigment storage in Kupffer cells at a dosage of 45 mg MBC/kg-day (Donaubauer, 1982). The lowest mouse NOEL was 25 mg MBC/kg-day. In the rat, MBC caused pericholangitis/cholangiohepatitis, increased serum alkaline phosphatase and glutamic pyruvic transaminase activity at 25 mg MBC/kg-day, with a 2-year NOEL of 4.9 mg MBC/kg-day (Sherman, 1972b). Dogs dosed repetitively with benomyl and/or MBC exhibited cirrhosis or fatty livers at termination, and increased serum alkaline phosphatase and elevated cholesterol at various sampling times during the 2-year studies (Sherman, 1970; Sherman, 1972a). The 1-year NOELs for hepatotoxicity in dogs were 15 mg of benomyl/kg-day (Sherman, 1970), and 2.6 mg of MBC/kg-day (Sherman, 1972a). The lowest NOEL, in benomyl equivalents, was thus 2.6 mg MBC/kg-day x 1.5, or 4 mg benomyl/kg-day (Sherman, 1972a).

Both dog studies were conducted by the same investigator in the same laboratory, and the NOELs and LOELs were a function of dose selection before the experiments were conducted. The highest NOEL (in benomyl equivalents) below the lowest LOEL (in benomyl equivalents) for hepatotoxicity was determined as follows. As the LOEL in the 1972a dog study [13.5 x 1.5 = 20.2 mg/kg-day in benomyl equivalents] was above the NOEL in the 1970 dog study (15 mg benomyl/kg-day), the 1970 dog study NOEL, 15 mg benomyl/kg-day, was the NOEL for potential chronic exposure of dogs to benomyl.

The lowest NOEL for repetitive exposure to MBC was in a combined chronic toxicity/oncogenicity study in the rat (Sherman, 1972b). The NOEL in benomyl equivalents was 4.9 mg MBC/kg-day x 1.5, or 7.4 mg benomyl/kg-day, with a LOEL of 37.5 mg benomyl/kg-day. However, it's important to take the entire database into consideration, rather than simply selecting the lowest NOEL as the regulatory endpoint.

The factors considered in the selection of the critical NOEL were 1) the effect of duration of exposure on hepatotoxicity of benomyl, 2) whether there were species differences in sensitivity, and 3) the effect of dose selection on the magnitude of the NOEL. In both the rat and the dog, the dose at which hepatotoxicity was manifested at 90 days (Igbedioh and Akinyele, 1992; Sherman, 1968a) was essentially the same as the LOELs for chronic exposure in the respective laboratory animals. Thus, increasing the duration of the dosing regime did not seem to affect the level at which hepatotoxicity occurred. The LOEL in one chronic dog study (20.2 mg/kg-day in benomyl equivalents) was only about half as great as the 2-year LOEL (37.5 mg benomyl/kg-day) in the chronic rat study. This indicated that the dog was at least as sensitive to benomyl as the rat with regards to hepatotoxicity. Indeed, the NOEL for hepatotoxicity in that chronic dog study (4 mg benomyl equivalents/kg-day; Sherman, 1972a) was less than the chronic rat NOEL (7.4 mg benomyl/kg-day; Sherman, 1972b). Thus, the NOELs in each of the studies were functions of dose selection. The highest NOEL (in benomyl equivalents) below the lowest LOEL (in benomyl equivalents) for hepatotoxicity in either species

was 15 mg/kg-d. Consequently, the critical NOEL, 15 mg benomyl/kg-day, used to assess margins of exposure for potential annual exposure to benomyl came from the acceptable dog study (Sherman, 1970).

The USEPA RfD of 0.05 mg/kg-day was based on a NOEL of 5 mg/kg-day for decreased weanling weights from a three-generation rat reproduction study (Sherman, 1968). The study was not acceptable to DPR under FIFRA guidelines because of inadequate group size and lack of feed analysis despite demonstrable instability of the test article.

Oncogenicity

The oncogenicity of benomyl and/or MBC in mice was indicated by increases in liver tumors in females (Weichman, 1982; Beems *et al.*, 1976; Wood, 1982), in males (Weichman, 1982), and ovarian tumors (Donaubauer, 1982). The mouse liver tumors described in these studies included hepato-adenomas, hepatocarcinomas, and relatively rare anaplastic hepatoblastomas. There was no evidence of oncogenicity in the rat. However, positive evidence for oncogenicity in one species (mouse) and genotoxicity test results demonstrating the potential of MBC to interact with DNA indicate a weight of evidence which is sufficient to warrant a quantitative risk assessment.

Although the oncogenicity of benomyl was indicated in several mouse studies, all of the studies had scientific flaws which made deriving a potency factor difficult. The specific problem in each study was that the high dose had been adjusted during the course of the studies. The USEPA derived their upper-bound potency factor ($q_1^* = 4.2 \times 10^{-3}$) from the incidence of hepatocellular carcinomas in female mice dosed with MBC (Wood, 1982). Several factors led DPR to the selection of a different study (Wiechman, 1982) as the basis for conducting a quantitative risk assessment: 1) This was the only study in mice which reported clear increases in tumors at dosages that were not hepatotoxic. 2) Female CD-1 mice have a low spontaneous incidence of hepatocellular tumors. 3) The data from this study provided the best fit, compared to the other studies, with the linear multistage model.

In accordance with National Toxicology Program guidelines (McConnell *et al.*, 1986), the incidences of hepatocellular adenomas and carcinomas in female mice (Table 4) were combined and used in calculating the potency of benomyl in the mouse study (Wiechman, 1982). An interspecies scaling factor, $(\text{body weight})^{3/4}$, was used to adjust for species differences, assuming a body weight of 70 kg for humans and 0.03 kg for mice. The maximum likelihood estimate (MLE) for human cancer potency was: $q_1 = 2.8 \times 10^{-3} (\text{mg/kg-day})^{-1}$; with an upper bound (95% confidence level) $q_1^* = 4.3 \times 10^{-3} (\text{mg/kg-day})^{-1}$.

B. EXPOSURE ASSESSMENT

The occupational exposure assessment was conducted by the Worker Health and Safety Branch of the Department of Pesticide Regulation (Haskell and Mehler, 1999), and is included in Appendix A.

According to the USEPA labels, all persons handling benomyl products, except those for home use, are required to wear long-sleeved shirts, long pants or coveralls, full body chemical-resistant clothing, waterproof gloves, and chemical-resistant footwear plus socks, and a dust/mist filtering respirator (Haskell and Mehler, 1999). In addition, mixer/loaders must also wear a chemical-resistant apron. A closed system is required for the transfer of the liquid mixture from the mix tank to the application tank. The proposed California regulations allow employees mixing and loading category III pesticides to substitute long-sleeved shirts and long pants or coveralls, and shoes and socks for the label-required personal protective equipment.

Applicators must wear a full body chemical-resistant suit, respirator, and eye protection; unless they use equipment with vehicle-mounted spray nozzles directed downward and located below the level of the applicator. Applicators operating equipment with closed cabs and positive pressure filtered air systems are not required to wear the chemical-resistant suit, respirator or eye protection, but must wear chemical-resistant gloves when exiting the cab or cockpit. Flaggers must be in a totally enclosed cab.

Occupational Exposure

Table 13 summarizes the estimated exposure dosages for various worker groups. Each of the values represents the total absorbed dosage from all routes (Haskell and Mehler, 1966). The Average Annual Daily Dosage (AADD) is based on 6 - 60 workdays per year (depending on the task); Lifetime Average Daily Dosage (LADD) assumes 40 years on the job. All agricultural estimates assumed an application rate of 1 pound active ingredient per acre. Occupational exposure estimates were derived from the USEPA Pesticide Handlers Exposure Database and from surrogate studies (Haskell and Mehler, 1999). Average potential daily exposures ranged from 1.3 µg/kg-day for ground applicators working with strawberries to 66.5 µg/kg-day for mixer/loaders associated with aerial applications on almonds. The potential AADDs ranged from 0.05 µg/kg-day for airblast applicators working with stone fruit to 3 µg/kg-day for field workers associated with wine grapes. Potential LADDs ranged from 0.03 µg/kg-day for airblast applicators working with stone fruit to 1.6 µg/kg-day for field workers associated with wine grapes. Prior to 1999, benomyl was available for home use. However, the label has changed so that home use is no longer permissible. Consequently, that exposure scenario is no longer considered in this document.

Table 13- Potential average exposures to benomyl from conducting various work tasks (Haskell and Mehler, 1999).

Work Task	ADD ^a ($\mu\text{g}/\text{kg}\text{-day}$)	AADD ^b ($\mu\text{g}/\text{kg}\text{-day}$)	LADD ^c ($\mu\text{g}/\text{kg}\text{-day}$)
Mixer/Loaders			
air blast- stone fruit	6.1	0.1	0.05
aerial applications- almonds	66.5	2.7	1.5
ground applications- strawberries	1.7	0.1	0.06
Applicators			
air blast- stone fruit	3.1	0.05	0.03
aerial applications- almonds	7.2	0.3	0.2
ground applications- strawberries	1.3	0.08	0.04
Flaggers			
	4.2	0.2	0.09
Harvesters			
strawberries	3.5	0.6	0.3
Field workers			
table grapes	42.1	2.4	1.3
wine grapes	51.6	3.0	1.6

- a/ The Absorbed Daily Dosage (ADD) was calculated assuming a) through the skin route a dermal absorption of 10% per day; and b) through the inhalation route a 50% retention of inhaled benomyl, with 100% absorption of retained benomyl (Haskell and Mehler, 1999). Body weight was assumed to be 75.9 kg for all work tasks by field workers.
- b/ The Average Annual Daily Dosage (AADD) was calculated by multiplying the ADD time the estimated number of annual 8-hour workdays for each work task, and dividing the product by 365 days/year.
- c/ Lifetime Average Daily Dosage = AADD x 40 yr working/75 yr life span.

Dietary Exposure

The Department of Pesticide Regulation (DPR) evaluates the risk of human exposure to an active ingredient in the diet using two processes: 1) use of residue levels detected in foods to evaluate the risk from total exposure, and 2) use of tolerance levels to evaluate the risk from exposure to individual commodities (see Tolerance Assessment). For the evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities (RACs), processed forms, and animal products (meat and milk) that have established USEPA tolerances. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

Consumption Data

The U.S. Department of Agriculture directs the Nationwide Food Consumption Survey (NCFS) and the Continuing Survey of Food Intakes by Individuals (CSFII). The NCFS is a geographically stratified probability sampling of U.S. Households and is conducted every 10 years (1977-78 and 1987-88). The CSFII is an annual survey which reflects the current consumption pattern and has a greater focus on consumption data for vulnerable populations subgroups (e.g., infants and children). The consumption analysis used the three-year data (1989-1990, 1990-1991, and 1991-1992) from the CSFII because they reflected current consumption patterns (USDA, 1989-1991).

Residue Data

The residue data for a dietary exposure assessment are based on DPR and federal monitoring programs, field trials, and survey studies. In the absence of data, surrogate data from the same crop group, as defined by USEPA, or USEPA tolerances are used. Residue levels that exceed established tolerances are not used in the dietary exposure assessments. Over-tolerance incidents are separately investigated by the DPR Pesticide Enforcement Branch. The potential risk from consuming commodities with residues over tolerance levels is evaluated by the Medical Toxicology Branch using an expedited acute risk assessment process.

DPR has two major sampling programs: priority pesticide and marketplace surveillance. Samples for the priority pesticide program are collected from fields known to have been treated with the specific pesticides. For the marketplace surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. The sampling strategies for both priority pesticide and marketplace surveillance are similar and are weighted toward such factors as pattern of pesticide use; relative number and volume of pesticides typically used to produce a commodity; relative dietary importance of the commodity; past monitoring results; and extent of local pesticide use. (DPR had two additional monitoring programs prior to 1991: The preharvest monitoring program routinely examined the levels of pesticides on raw agricultural commodities in the field at any time during the growth cycle. Commodities destined for processing were collected in the field no more than 3 days prior to harvest, at harvest, or post-harvest before processing.)

The U. S. Food and Drug Administration (FDA) has three monitoring programs for determining residues in food: (1) regulatory monitoring, (2) total diet study, and (3) incidence/level monitoring. For regulatory monitoring, surveillance samples are collected from individual lots of domestic and imported foods at the source of production or at the wholesale level. In contrast to the regulatory monitoring program, the total diet study monitors residue levels in the form that a commodity is commonly eaten or found in a prepared meal. The incidence/level monitoring program is designed to address specific concerns about pesticide residues in particular foods.

The U. S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. Several states, including California, collect samples at produce markets and chain store distribution centers close to the consumer level. The pesticide and produce combinations are selected based on the toxicity of the pesticide as well as the need for residue data to determine exposure. In addition, USDA is responsible for the National Residue Program provides data for potential pesticide residues in

meat and poultry. These residues in farm animals can occur from direct application, or consumption of commodities or by-products in their feed.

Monitoring for benomyl was not included in DPR surveillance programs for raw agricultural commodities (RACs) from 1987-1995. Data came from the FDA monitoring programs, USDA's PDP program, field studies, and tolerances (Appendix C).

Tolerances are presently established at 50 ppm for residues of benomyl on bean vine forage; 35 ppm on pineapples; 15 ppm on apricots, sugar beet tops, Brussels sprouts, cherries, nectarines, peaches, peanut forage and hay, plums, rice straw, and wheat straw; 10 ppm on Chinese cabbage, citrus fruits, dandelions, grapes, mushrooms, and watercress; 7 ppm on apples, blackberries, blueberries, boysenberries, currants, dewberries, loganberries, pears, and raspberries; 6 ppm on turnip greens; 5 ppm on rice, strawberries, and tomatoes; 3 ppm on avocados, celery, mangoes, and papayas; 2 ppm on beans and peanut hulls; 1 ppm on almond hulls, bananas, cucumbers, melons, pumpkins, summer and winter squash; 0.2 ppm on barley grain and straw, sugar beets, broccoli, cabbage, carrots, cauliflower, collards, corn, eggplant, garlic, kale, kohlrabi, mustard greens, nuts, oats and oat straw, peanuts, peppers, pistachios, poultry livers, rutabagas, rye and rye straw, soybeans, spinach, sweet potatoes, turnips and wheat; 0.1 ppm on cattle, eggs, goats, hogs, horses, milk, poultry, and sheep (Code of Federal Regulations, 1995).

Daily (Acute) Exposure

Estimates of potential daily dietary exposure used the highest measured residue values at or below the tolerance for each commodity. For commodities with residues at or below the minimum detection limit (MDL), a value equal to the MDL is assigned to each commodity. When the residue values are derived from monitoring programs, the default assumption is that the data represent high end residue levels in the diet. The use of the data does not account for the potential change in residue levels due to (1) washing and peeling, and (2) food preparation and processing (e.g., cooking and canning).

Daily dietary exposure analyses were conducted using the Exposure-4™ software program developed by Technical Assessment Systems, Inc (TAS). The Exposure-4™ software program estimates the distribution of user-day (consumer-day) exposures for the overall U.S. population and specific population subgroups (TAS, 1996a). A user-day is any day in which at least one food from the specific commodity list is consumed. The consumption analysis uses individual food consumption data as reported in the 1989-1991 USDA Continuing Surveys of Food Intake of Individuals (USDA, 1989-91). Potential daily ingestion of benomyl for all labeled uses, based on the 95th percentile of user-day exposure for all population subgroups, ranged from 11 to 39 µg/kg-day (Table 14). Nursing infants, less than 1 year of age had the highest potential daily dietary exposure to benomyl when all food uses were considered.

Annual (Chronic) Exposure

Estimates of potential annual dietary exposure used the average of measured and "below the detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to one half (50%) of the detection limit for each RAC. The same assumptions that were used to estimate potential acute dietary exposure apply to potential chronic dietary exposures. In addition, it is assumed that a commodity with the average calculated residue is consumed every day at an annual average level (dosage).

The potential annual dietary exposure was calculated using the Exposure-1™ software (TAS, 1996b). The food consumption data for the annual analysis were also derived from the USDA Continuing Surveys of Food Intake of Individuals (USDA, 1989-91). The mean potential annual dietary exposure for all population subgroups ranged from 0.7 to 3.2 µg/kg-day (Table 14). Children, 1 to 6 years of age, had the highest potential exposures. The crops and food groups contributing more than 10% to the dietary exposure to benomyl for the various population subgroups were: tomatoes, peaches, and winter squash.

Table 14 - Potential daily and annual dietary exposures to benomyl residues.

Population Subgroup	Exposure Dosage (µg/kg-day)	
	Daily ^a	Annual ^b
U.S. Pop. (All Seasons)	16	1.8
Western Region	17	1.7
Pacific Region	18	2.0
Nursing Infants (<1 yr)	39	1.9
Non-Nursing Infants (<1 yr)	35	0.7
All Infants	38	1.6
Children (1-6 yrs)	33	3.2
Children (7-12 yrs)	23	2.7
Female (13+ yrs/pregnant/not nursing)	10	1.4
Female (13+ yrs/nursing)	30	1.7
Females (13-19 yrs/not pregnant/not nursing)	15	1.8
Female (20+ yrs/not pregnant/not nursing)	13	1.6
Females (13-50 yrs)	13	1.6
Males (13-19 yrs)	11	1.7
Male (20+ yrs)	12	1.5
Seniors (55+ yrs)	13	1.6
Workers (16+ yrs)	12	- ^c
Hispanics	17	2.1
Non-Hispanic Whites	16	1.8
Non-Hispanic Blacks	19	1.6
Non-Hispanic Other	24	2.2

a/ Calculated from highest measured residues, less than tolerance (Appendix C). Based on the 95th percentile for user-day exposures in all population subgroups.

b/ Calculated using the arithmetic mean of measured residues.

c/ Computer program does not provide a method to calculate this value.

Combined Occupational and Dietary Exposure

Occupational exposures do not constitute the sole source of an absorbed dose of benomyl. Dietary exposure may also contribute to the overall body burden of benomyl in workers. The potential daily and annual dietary exposures were added to the mean occupational exposure to obtain an estimate of the total exposure to benomyl. The potential dietary exposure of the population subgroup, females, 20+ years of age, was chosen for the purposes of estimating combined occupational and potential dietary exposures. The choice was based on two factors: 1) Occupational exposures were derived from actual measurements or surrogate data involving male agricultural workers, but females from this population subgroup can also perform the same tasks. 2) The dietary exposure values, although greater than males, are approximately the same as those of any other population subgroup which might contribute to the agricultural work force. The potential daily dietary exposure of this population subgroup (females, 20+ years of age) was 13 µg/kg-day, and the potential annual dietary exposure was 1.6 µg/kg-day. These values were added to the mean estimated occupational exposures (Table 15).

Table 15- Combined potential average occupational and dietary exposures to benomyl.

Work Task	ADD ^a (µg/kg-day)	AADD ^b (µg/kg-day)	LADD ^c (µg/kg-day)
Mixer/Loaders			
air blast- stone fruit	19	1.7	1.7
aerial applications- almonds	79	4.3	3.1
ground applications- strawberries	14	1.7	1.7
Applicators			
air blast- stone fruit	16	1.7	1.6
aerial applications- almonds	20	1.9	1.8
ground applications- strawberries	13	1.7	1.6
Flaggers			
	17	1.8	1.7
Harvesters			
strawberries	16	2.2	1.9
Field workers			
table grapes	55	4.0	2.9
wine grapes	64	4.6	3.2

- a/ The Average Daily Dosage (ADD) was calculated assuming a dermal absorption of 10% per day, and 50% retention through the inhalation route, with 100% absorption of benomyl (Haskell and Mehler, 1999). Body weight was assumed to be 75.9 kg for all work tasks by field workers. Exposure for both types of workers includes 13 µg/kg-day for daily dietary consumption of benomyl.
- b/ The Average Annual Daily Dosage (AADD) was calculated by multiplying the ADD time the estimated number of annual 8-hour workdays for each work task, and dividing the product by 365 days/year. Includes 1.6 µg/kg-day for annual dietary consumption of benomyl.
- c/ Lifetime Average Daily Dosage = Occupational AADD x 40/75 + 1.6 µg/kg-day for annual dietary consumption.

C. RISK CHARACTERIZATION

The developmental (post-implantation loss) and hepatotoxic effects observed in laboratory animals exposed to benomyl are considered to have a biological threshold. Exposure below a certain level is not expected to cause adverse effects. The Margin of Exposure (MOE) for exposure to benomyl is calculated as the ratio of an appropriate critical NOEL established in animal studies to the potential exposure dosage estimated for human populations.

$$\text{Margin of Exposure} = \frac{\text{NOEL}}{\text{Exposure Dosage}}$$

The oncogenic potential for benomyl or MBC to produce neoplasms in laboratory animals (and humans) was not considered to have a threshold. Thus, the excess lifetime risk of cancer is calculated by multiplying the Lifetime Average Daily Dosage times the human cancer potency factor [MLE = $2.8 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$; 95th upper bound = 4.3×10^{-3}].

$$\text{Excess Risk of Cancer} = [\text{LADD}] \times [\text{potency factor}]$$

Occupational Exposure

The margins of exposure for mean, potential, daily exposure to benomyl, based on a critical NOEL of 15 mg/kg-day for post-implantation loss in rabbits, ranged from 225 for mixer/loaders involved in aerial applications to almond groves to 12,000 for ground applications of benomyl on strawberries (Table 16). MOEs for average annual exposures to benomyl, based on a critical NOEL of 15 mg/kg-day for hepatotoxicity in dogs, ranged from 5,000 for field workers with wine grapes to 300,000 for airblast applicators working with stone fruits.

The maximum likelihood estimates of excess lifetime risks of cancer, based on a $q_1 = 0.0028 \text{ (mg/kg-day)}^{-1}$ for hepatocellular adenomas and carcinomas in female mice, ranged from 0.1×10^{-6} for airblast applicators working with stone fruits to 4×10^{-6} for field workers with grapes (Table 16). The 95th upperbound estimate of the excess lifetime risk of cancer ranged from 0.1×10^{-6} to 6×10^{-6} based on a q_1^* of $0.0043 \text{ (mg/kg-day)}^{-1}$ for these same work tasks.

Table 16- Margins of Exposure (MOE) and excess lifetime risks of cancer from potential average exposures to benomyl from conducting various work tasks.

Work Task	MOE ^a (acute)	MOE ^b (annual)	Cancer Risk ^c (x10 ⁻⁶)	Cancer Risk ^d (x10 ⁻⁶)
Mixer/Loaders				
air blast- stone fruit	2,000	150,000	0.1	0.1
aerial applications- almonds	225	6,000	4	6
ground applications- strawberries	9,000	150,000	0.2	0.3
Applicators				
air blast- stone fruit	5,000	300,000	0.1	0.1
aerial applications- almonds	2,000	50,000	0.6	
ground applications- strawberries	12,000	188,000	0.1	0.1
Flaggers				
	4,000	75,000	0.3	0.4
Harvesters				
strawberries	4,000	25,000	0.8	1.2
Field workers				
table grapes	356	6,000	4	6
wine grapes	290	5,000	4	6

a/ Based on critical NOEL = 15 mg/kg-day for post implantation loss in a rabbit study (Feussner, 1985).

$$\text{MOE} = \frac{\text{NOEL (15,000 } \mu\text{g/kg-day)}}{\text{ADD}}$$

b/ Based on a critical NOEL = 15 mg/kg-day hepatotoxicity in a dog study (Sherman, 1970).

$$\text{MOE} = \frac{\text{NOEL (15,000 } \mu\text{g/kg-day)}}{\text{AADD}}$$
 (rounded to nearest thousand)

c/ Maximum likelihood estimate of the excess lifetime risk of cancer is based on a $q_1 = 0.0028$ (mg/kg-day)⁻¹.

d/ Upper bound estimate of the excess lifetime risk of cancer is based on a $q_1 = 0.0043$ (mg/kg-day)⁻¹.

Dietary Exposure

Daily Exposure

The MOEs for potential daily dietary exposure to benomyl, based on an acute critical NOEL of 15 mg/kg for post-implantation loss in rats, ranged from 385 to 1,400 (Table 17).

Annual Exposure

The MOEs for annual dietary exposure to benomyl, based on a critical NOEL of 15 mg/kg-day for hepatotoxicity in dogs, ranged from 5,000 for children (1-6 yrs) to 21,000 for non-nursing infants less than 1 yr of age (Table 17).

Lifetime Exposure

The maximum likelihood estimate of the excess lifetime risk of cancer for the U.S. Population was 5×10^{-6} . The 95th upperbound estimate of the excess lifetime risk of cancer for the U.S. Population was 8×10^{-6} .

Table 17- Margins of exposure for potential daily and annual dietary exposures to benomyl residues.

Population Subgroup	Margin of Exposure	
	Daily ^a	Annual ^b
U.S. Pop. (All Seasons)	938	8,000
Western Region	882	9,000
Pacific Region	833	8,000
Nursing Infants (<1 yr)	385	8,000
Non-Nursing Infants (<1 yr)	429	21,000
All Infants	394	9,000
Children (1-6 yrs)	455	5,000
Children (7-12 yrs)	652	6,000
Female (13+ yrs/pregnant/not nursing)	1,500	11,000
Female (13+ yrs/nursing)	500	9,000
Females (13-19 yrs/not pregnant/not nursing)	1,000	8,000
Female (20+ yrs/not pregnant/not nursing)	1,200	9,000
Females (13-50 yrs)	1,200	9,000
Males (13-19 yrs)	1,400	9,000
Male (20+ yrs)	1,300	10,000
Seniors (55+ yrs)	1,200	9,000
Workers (16+ yrs)	1,300	-
Hispanics	882	7,000
Non-Hispanic Whites	938	8,000
Non-Hispanic Blacks	938	9,000
Non-Hispanic Other	625	7,000

a/ Based on critical NOEL = 15 mg/kg-day for post implantation loss in a rabbit study (Feussner, 1985).
 $MOE = \frac{NOEL (15,000 \mu g/kg\text{-day})}{ADD}$

b/ Based on a critical NOEL = 15 mg/kg-day hepatotoxicity in a dog study (Sherman, 1970).
 $MOE = \frac{NOEL (15,000 \mu g/kg\text{-day})}{AADD}$ (rounded to nearest thousand)

Combined Dietary and Occupational Exposure

MOEs for potential combined daily occupational and dietary exposure to benomyl ranged from 190 for mixer/loaders involved in aerial applications on almonds, to 1,000 for ground application on strawberries (Table 18). MOEs for potential combined annual exposure ranged from 3,000 to 9,000 for several work categories. Maximum likelihood estimates of excess lifetime risks of cancer from combined occupational and dietary exposures ranged from 3×10^{-6} to 7×10^{-6} . The upper bound estimate of the lifetime risk of cancer for the same groups ranged from 4×10^{-6} to 10×10^{-6} .

Table 18- Margins of exposure for combined daily occupational and dietary exposures to benomyl.

Work Task	MOE ^a (daily)	MOE ^b (annual)	Cancer Risk ^c ($\times 10^{-6}$)	Cancer Risk ^d ($\times 10^{-6}$)
Mixer/Loaders				
air blast- stone fruit	789	9,000	5	7
aerial applications- almonds	190	3,000	9	13
ground applications- strawberries	1,000	9,000	5	7
Applicators				
air blast- stone fruit	938	9,000	4	7
aerial applications- almonds	750	8,000	5	8
ground applications- strawberries	1,000	9,000	4	7
Flaggers				
	882	8,000	5	7
Harvesters				
strawberries	938	7,000	5	8
Field workers				
table grapes	273	4,000	8	12
wine grapes	234	3,000	9	14

a/ Based on critical NOEL = 15 mg/kg-day for post implantation loss in a rabbit study (Feussner, 1985).

$$\text{MOE} = \frac{\text{NOEL (15,000 } \mu\text{g/kg-day)}}{\text{ADD}}$$

b/ Based on a critical NOEL = 15 mg/kg-day hepatotoxicity in a dog study (Sherman, 1972a).

$$\text{MOE} = \frac{\text{NOEL (15,000 } \mu\text{g/kg-day)}}{\text{AADD}} \quad (\text{rounded to nearest thousand})$$

c/ Maximum likelihood estimate of the excess lifetime risk of cancer is based on a $q_1 = 0.0028$ (mg/kg-day)⁻¹ x LADD.

d/ Upper bound estimate of the excess lifetime risk of cancer is based on a $q_1 = 0.0043$ (mg/kg-day)⁻¹ x LADD.

RISK APPRAISAL

Risk assessment is a process used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance may occur in humans under the specific exposure conditions. Every risk assessment has inherent uncertainties and limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are, by default, incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. These postulates, in turn, generate uncertainties in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, all risk assessments have similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the availability of the data and the exposure scenarios being assessed. Risk, the probability of a compound causing an adverse health effect, is a product of the potential exposure and the toxicity of a compound. Estimation of both of these aspects involves varying degrees of uncertainty, which can affect the accuracy of the risk characterization. Overestimates of potential exposure or toxicity will lead to excessive projections of risk, while under valuation of these aspects would result in underestimates of risk.

A. TOXICOLOGY

In the absence of scientific evidence to the contrary, effects reported in laboratory studies are expected to occur in humans at similar dosages. Specific areas of uncertainty associated with the toxicology of benomyl and MBC are delineated in the following discussion.

Acute Toxicity

The regulatory endpoint selected for acute exposures to benomyl was based on post-implantation loss in pregnant rabbits given MBC by gavage. This developmental endpoint for exposure to MBC or benomyl may only be relevant to women of child-bearing age. The assumption that all other population subgroups are as sensitive as women of child-bearing age results in MOEs that protect the health of these other subgroups for other adverse effects that may occur at higher dosages. As developmental toxicity may be manifested as the result of a single dose (Schardein, 1985; Ogata *et al.*, 1984; USEPA, 1991), it was assumed, in the absence of data to the contrary, that the observed effects were elicited from a single, bolus dose. It should be noted that blood levels of MBC measured during the 24 hours following dosing were 77% higher subsequent to gavage dosing than after feeding at a similar dosage (Staples, 1980, 1982). Human dietary exposures would more closely approximate the feeding exposure, making the 15 mg/kg critical NOEL derived from gavage dosing a worst-case scenario.

With regard to non-dietary exposures, it should be noted that the critical NOEL used for assessing potential short-term exposures to benomyl is based on an oral study. The principal route of occupational exposure to humans was dermal (Haskell and Mehler, 1999). In one study, blood levels following dermal exposure to toxins absorbed through the skin were much less than the blood levels of those same compounds when absorbed through the gut (Wester and Maibach, 1983). Further, the acute critical NOEL is derived from a laboratory animal study using MBC by gavage. Although, benomyl is converted to MBC in the body, the conversion is not likely to occur instantaneously. This is especially true of a dermal dose which does not pass through the liver before going to the rest of the body. Consequently, the blood levels of MBC achieved in a gavage dose of MBC would be likely to be much greater than with a similar

dosing regimen using benomyl. As the toxicity of benomyl appears to be principally due to the metabolite MBC (Lim and Miller, 1997), the MOEs for occupational exposures may be greater.

The database for one of the major breakdown products of benomyl, *n*-butyl isocyanate, is not particularly extensive. However, examination of the toxicological database for benomyl and MBC indicates there is not much difference in the toxicological effects of the two compounds on an equimolar basis in acute, subchronic, chronic, or lifetime exposure studies in laboratory animals. If there were highly significant toxicological effects of *n*-butyl isocyanate, the results of those studies involving benomyl should be markedly different from those that utilized MBC. The fact that the results are not significantly different argues that effects of *n*-butyl isocyanate produced by metabolism of benomyl *in vivo* are also insignificant.

Chronic Toxicity.

The uncertainties noted above with regard to the importance of route to the toxicity of benomyl in acute exposures obtain with regard to chronic occupational/ residential exposures, which arise from repeated dermal dosing. Based on these uncertainties, the MOEs for long-term occupational exposures may be greater than the calculated values presented in the Risk Characterization. The critical NOEL for hepatotoxicity in dogs (15 mg benomyl/kg-day) was greater than the NOEL for hepatotoxicity for lifetime exposure in the rat (7.4 mg benomyl/kg-day). However, the critical NOEL (dogs) was substantially less than the LOEL for hepatotoxicity, 37.5 mg benomyl/kg-day, in rats (see Hazard Identification section). Nonetheless, should the true NOEL for hepatotoxicity in rats be less than the critical NOEL for hepatotoxicity in dogs (which was used as the regulatory endpoint), the MOEs for long term occupational exposures would be less than those values presented in the text.

Oncogenicity

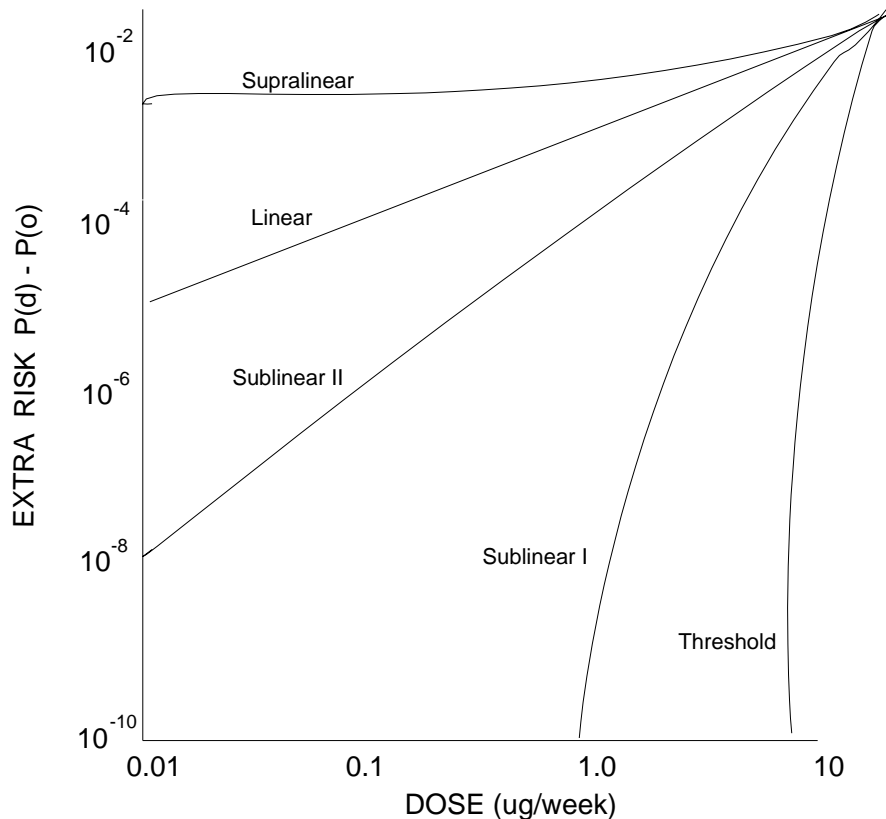
Although the oncogenicity of benomyl/MBC was only demonstrated in mice, liver tumors were induced in both sexes and in different strains of mice (Weichman, 1982; Beems *et al.*, 1976; Wood, 1982). Mouse ovarian tumors were also noted (Donabauer, 1982). Positive results from various types of genotoxicity studies indicated the potential of benomyl/MBC to disrupt the genome (Russell and Rickard, 1986c; Summers, 1981a; Jotz *et al.*, 1980; Sasaki, 1990; Sasaki, 1988; Evans and Mitchell, 1980), so the weight of evidence clearly indicated oncogenic potential for benomyl and the metabolite, MBC.

It was possible to extrapolate to the possible oncogenic effects of low doses of benomyl potentially experienced by humans by fitting a mathematical model to the dose-response data in the laboratory animal studies. However, the true shape of the dose-response curve at dosages several orders of magnitude below the range of measurable values cannot be determined experimentally (NAS, 1983).

The dose-response of benzopyrene (a known human carcinogen) is presented as an example of the uncertainty in the shape of the dose response curve in the low dose range (NAS, 1983). Figure 2 illustrates curves generated by five different mathematical models which fit the experimental data for this chemical in the measurable range equally well. In the low dose range, where the effects cannot be determined experimentally, the predicted curves are very different. These mathematical models are not equally plausible from a biological standpoint. Most scientists agree that the supra-linear model can be discarded because a biological mechanism that would give rise to that type of a low dose response is hard to imagine. The threshold model is based on the assumption that below a particular dose there is no adverse

effect. The linearized multistage model, which was used to estimate the oncogenic risks of benzopyrene, represents a theoretical upper bound on the plausible risk of cancer caused by potential exposures to the chemical. An upperbound estimate of the linearized multistage model begins to approach supralinear models.

Figure 2. Results of alternative extrapolation models for the same experimental data. The dose response functions were developed for data from a benzopyrene carcinogenesis experiment with mice (NAS, 1983).



B. EXPOSURE

Occupational

All measurements of occupational exposure were derived from the Pesticide Handlers Exposure Database (PHED), or surrogate data (Haskell and Mehler, 1999). Surrogate data carry a greater degree of uncertainty than would data derived from actual measurements using benomyl. The principle difficulty associated with the use of PHED to estimate exposure data is that the data subsets which are combined by the program to form work categories are not homogeneous (van Hemmen, 1992). For example, one source of variability is that each of those studies had a different minimum detection level for the analytical method. It should be noted that the detection of dermal exposure to the body regions was not standardized. Some studies observed exposure to only selected body regions, such as the hands, arms and face, with other body regions considered 100% protected from exposure by work clothing. Other studies had more extensive dermal measurements. Consequently, the subsets derived from the database for dermal exposure have different numbers of observations for each of the body regions. Finally, the PHED database is predicated on the relationship between amount of

pesticide handled, and the degree of occupational exposure. Yet, within the data set used to estimate exposures for groundboom applications without the presence of a cab there is no correlation between the amount of pesticides being used and the amount of dermal or inhalation exposures that workers receive. The net effect of this lack of correlation between exposure and the amount of chemical used is an inability to predict, with accuracy, what exposures any worker will receive in a given work category.

When PHED is used for estimating potential acute (single day) occupational exposures, the only data point which can be provided is the average exposure value. Because the variability in each of the data subsets in a given category is unrelated to that in any of the other data subsets, there is no manner in which the overall variability in exposure can be estimated. Yet, there is variability in worker exposure even though each individual conforms their activities to label-approved personal protective equipment and labor practices. When the average exposure value is used, this represents the potential exposures of most of the workers. The amount of exposure for the other workers (potentially up to 50%), who also follow label requirements, would be greater- though the magnitude of the exposure cannot be calculated. Therefore, margins of exposure for these workers would probably be lower.

Potential lifetime occupational exposure estimates depend upon the assumption that an individual would maintain the same work category for 40 years, and would spray the same product to control fungal infestations on a few days every few months each year during that period of time (Haskell and Mehler, 1999). The use of an LADD to approximate lifetime exposure from intermittent doses of a chemical may underestimate risk 2 to 5 fold, but is more likely to overestimate it by several orders of magnitude (Murdoch *et al.*, 1992; Murdoch and Krewski, 1988; Kodell *et al.*, 1987; Morrison, 1987).

Dietary

Some practices, such as the sampling of RACs as composites, could lead to underestimates of potential daily dietary exposure. In general, though, sampling procedures, default assumptions for non-detectable residue levels, assumptions on the fate of residues on commodities, and assumptions regarding the percentage of crops treated with benomyl are likely to contribute to an overestimation of the potential dietary exposure. The consumption data contained in the USDA survey may not be an accurate representation of actual dietary consumption by each of the population subgroups. Coding and reporting errors, response and sampling bias, and variation in culinary habits over the sampling period resulted in uncertainties in consumption data which can lead to either over- or underestimates of exposure (Bingham, 1991).

The probability of the dietary contribution to the daily exposure of an individual in a given population subgroup is a product of the probabilities that 1) an individual would consume a sufficient amount of the commodities to be in the 95th percentile of daily dietary exposure dosages and 2) the commodities would all contain the maximum residue levels. Clearly, this is an overestimate of daily dietary exposure.

The potential combined daily dietary and occupational exposures indicated in Table 13 are probably over-estimations of the actual exposures, as it is improbable that all of the assumptions made in the calculation of combined exposure dosage would be met. It is unlikely that the agricultural workers or residential applicators engaged in benomyl application would also be in the 95th percentile of consumption of commodities, each commodity contaminated with maximum benomyl residues.

C. RISK CHARACTERIZATION

When the NOEL for an adverse effect is derived from a laboratory animal study, a calculated MOE of 100 is generally considered adequate for protection against potential toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that the least sensitive human is 10 times more sensitive to the effects of a toxin than are laboratory animals (Davidson *et al.*, 1986; Dourson and Stara, 1983, 1985; USEPA, 1986b). If the critical NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor which assumes there is only a 10-fold difference between the least sensitive and most susceptible human.

D. FEDERAL FOOD QUALITY PROTECTION ACT

The Federal Food Quality Protection Act of 1996 (FQPA) requires USEPA to set health-based tolerances using an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data with respect to exposure and toxicity to infants and children. A different safety factor may be used only if, on the basis of reliable data, such a factor will be safe for infants and children. In addition, USEPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with mechanisms of toxicity in common; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

Pre-/Post-Natal Sensitivity

FQPA requires USEPA to set health-based tolerances using an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data with respect to exposure and toxicity to infants and children. As discussed in the Hazard Identification portion of this document, both benomyl and its metabolite, MBC, have adverse pre-natal effects. The compounds were associated with a wide spectrum of developmental toxicity in three species of laboratory animals (mouse, rat and rabbit), ranging from the induction of major malformations to post-implantation loss (abortion). The regulatory endpoint used in this document for calculating the margins of exposure for potential daily exposures is based on post-implantation loss in rabbits.

Endocrine Effects

Although benomyl and MBC have been shown to adversely affect male reproduction, the mechanism of action does not appear to involve the endocrine system. Consequently, neither benomyl nor MBC would be subject to the provisions of FQPA dealing with “endocrine disrupters”.

Multiple Chemical (Cumulative) Exposure

Benomyl is a benzimidazole fungicide. It is unclear at this time if benomyl has any cumulative (i.e., combined) toxicity due to a common mechanism of toxicity with other benzimidazoles (with the exceptions of its metabolite MBC, also known as carbendazim; and thiophanate methyl which also forms carbendazim) or any other chemicals. Given the uncertainty about any potential combined toxicity, this risk assessment only addressed those factors which are specific to the toxicity of benomyl and MBC.

Aggregate Exposure

Benomyl and MBC are unlikely to become groundwater contaminants because of low water solubility and immobility in soil. Combined occupational and dietary exposures to benomyl had daily MOEs ranging from 234 to 1,000. Benomyl can also be used in residential gardening. The aggregate daily MOEs for dietary exposure and occupational exposures were all greater than 3,000 (Table 18).

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

USEPA is responsible under the Federal Food, Drug, and Cosmetic Act (FFDCA) for setting tolerances for pesticide residues in raw agricultural commodities (Section 408 of FFDCA) and processed commodities (Section 409 of FFDCA). A tolerance is the legal maximum residue concentration of a pesticide which is allowed on a raw agricultural commodity or processed food. The tolerances are established at levels necessary for the maximum application rate and frequency, and not expected to produce deleterious health effects in humans from annual dietary exposure (USEPA, 1991c). The data requirements for tolerances include: (1) residue chemistry, (2) environmental fate, (3) toxicology, (4) product performance such as efficacy, and (5) product chemistry (Code of Federal Regulations, 1996). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications and formulations proposed (USEPA, 1982).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (USEPA, 1997b,c). One major change was the removal of the Delaney Clause that prohibited residues of cancer-causing pesticides in processed foods. The tolerances must be health-based and the same standards are used to establish tolerances for both the raw agricultural commodities and their processed forms. FQPA required an explicit finding that tolerances are safe for children. USEPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless USEPA determined, based on reliable data, that a different margin would be safe. In addition, the evaluations of the tolerance must take into account: (1) aggregate exposure from all non-occupational sources, (2) effects from cumulative exposure to the pesticide and other substances with common mechanisms of toxicity, (3) effects of *in utero* exposure; and (4) potential for endocrine disrupting effects. (Discussion of these issues specific to benomyl is in the Risk Appraisal section.)

Under FQPA, USEPA is also required to reassess all existing tolerances and exemptions from tolerances for both active and inert ingredients by 2006 (USEPA, 1997d). Previously, USEPA reassessed tolerances as part of its reregistration and Special Review processes. In the evaluation of tolerances, the USEPA uses a tiered approach and the assessment includes all label-use commodities.

In California, USEPA established tolerances are evaluated under the mandate of Assembly Bill 2161, generally referred to as the Food Safety Act (Bronzan and Jones, 1989). The Act requires DPR to conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides. In these assessments, the tolerance for each specific commodity is evaluated individually and is discussed in the following sections. For a pesticide registered for use on a large number of commodities, tolerance assessments are conducted for only a group of selected fruits and vegetables. Generally, commodities are selected from all the uses based on the potential for high levels of exposure.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. The TAS Exposure-4® software program and the individual food consumption data as reported in the 1989-1991 USDA Continuing Surveys of Food Intake of Individuals (USDA, 1989-91) are used in this assessment. The acute tolerance assessment does not routinely address multiple commodities at the tolerance levels as the probability of consuming multiple commodities at the tolerance decreases as the number of commodities included in the assessment increases. Therefore, residue levels for benomyl were set equal to the tolerance, and the MOE, based on the upper 95th percentile for user-day exposures for each population subgroup was examined for the most highly consumed commodities (FDA, 1991). The MOEs ranged from 11 to 44,500 for population subgroups theoretically exposed to tolerance levels of benomyl residues on label-approved commodities (Table 19). Only the tolerances on the most frequently consumed commodities were examined, as it is assumed that the MOEs for lesser consumed commodities would be as great or greater.

The MOEs were over 100 for all population subgroups theoretically exposed to tolerance levels of residue on: apricots, avocados, bananas, barley, beans, blackberries, blueberries, boysenberries, broccoli, Brussels sprouts, cabbage, carrots, cattle, cauliflower, celery, Chinese Cabbage, collards, corn, cucumbers, currants, dewberries, eggplant, eggs, garlic, hogs, kale, kohlrabi, loganberries, mangoes, melons, milk, mushrooms, mustard greens, nectarines, nuts, oats, papayas, peanuts, peppers, pistachios, plums, poultry, pumpkins, rice, rutabagas, rye, sheep, soybeans, spinach, strawberries, sugar beets, summer and winter squash, sweet potatoes, tomatoes, turnips, and wheat. MOEs were 99 or less for at least two, but not all population subgroups (with sufficient consumption data) for theoretical exposure to tolerance levels of residues on: apples, grapes, oranges, peaches, pears, and pineapples.

C. ANNUAL EXPOSURE

An annual exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from FDA and DPR (formerly California Department of Food and Agriculture) pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990).

Table 19- MOEs for theoretical acute dietary exposure to tolerance levels of benomyl residues for the most highly consumed commodities^a

Agricultural Commodity	Tolerance (ppm)	Margin of Exposure (Range)^{a,b}
Apples	7	28 - 536
Apricots	15	284 - 11,500
Bananas	1	1,500 - 6,100
Brussels Sprouts	15	193 - 1,500
Carrots	0.2	5,500 - 44,500
Celery	3	2,700 - 11,300
Cherries	15	308 - 4,900
Grapes	10	52 - 664
Milk`	0.1	1,500 - 14,200
Mushrooms	10	737 - 2,900
Nectarines	15	116 - 476
Oranges	10	11 - 401
Peaches	15	64 - 534
Pears	7	55 - 1,600
Pineapples	35	19 - 231
Plums	15	129 - 608
Rice	5	492 - 1,800
Strawberries	5	1,200 - 23,600
Tomatoes	5	342 - 816

a/ Based on the 95th percentile of user-days for all population subgroups.

b/ Rounded to the nearest hundred if over one thousand.

VII. CONCLUSIONS

Occupational

Margins of exposure, based on current toxicity data, for mean daily occupational exposures were greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. When the mean short term occupational exposures were combined with potential daily dietary exposure, the MOEs still remained greater than 100.

Margins of exposure for annual occupational exposure, or combined occupational exposure and potential annual dietary exposure, were greater than 100. Maximum Likelihood Estimates (MLEs) of excess lifetime risks of cancer from occupational exposure to benomyl ranged from 0.1×10^{-6} to 4×10^{-6} , with 95th percentile upper bounds ranging from 0.1×10^{-6} to 6×10^{-6} . MLEs of excess lifetime risks of cancer from combined occupational and potential annual dietary exposure to benomyl ranged from 4×10^{-6} to 9×10^{-6} , with the 95th percentile upper bounds ranging from 7×10^{-6} to 14×10^{-6} .

Dietary

The margins of exposure for potential daily and annual dietary exposure all population subgroups were greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical. The maximum likelihood estimate of the excess lifetime risk of cancer for the U.S. Population was 5×10^{-6} , with a 95th percentile upperbound estimate of 8×10^{-6} .

Tolerances

Seven of the USEPA tolerances for benomyl on agricultural commodities provided margins of exposure less than 100 for theoretical daily dietary exposure to one or more population subgroups if commodities are consumed with residues at the tolerance level. Benomyl has adverse pre-natal effects, which should be taken into consideration when USEPA reviews the tolerance levels under the Food Quality Protection Act.

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APPENDIX A
TOXICOLOGICAL SUMMARY

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

BENOMYL AND MBC (PRINCIPAL BENOMYL METABOLITE)

SB 950-201, Tolerance # 294
Chemical Code 1552

August 14, 1986

Revised 11/6/86, 9/15/87, 5/16/89, 9/21/89,
10/9/90, 3/14/91, 12/18/91, 9/24/93, 2/15/95, 9/3/96, 10/01/97

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effect.
Chronic dog:	No data gap, possible adverse effect.
Oncogenicity, rat:	No data gap, no adverse effect.
Oncogenicity mouse:	No data gap, possible adverse effect.
Reproduction rat:	No data gap, possible adverse effect.
Teratology rat:	No data gap, possible adverse effect.
Teratology rabbit:	No data gap, possible adverse effect.
Gene mutation:	No data gap, possible adverse effect.
Chromo. aberration:	No data gap, possible adverse effect.
DNA damage:	No data gap, possible adverse effect.
Neurotoxicity:	Not required at this time.

NOTE: Toxicology one-liners are attached. ** Before the one-liner indicates an acceptable study.
Bold face of volume and record numbers indicates a possible adverse effect.

Previous versions of Summary by F. Martz, and J. Gee. Rectified with Library printout of 2/15/95 including record #'s up to 131147 (Document No. 294-161) and 900000+. 10/9/90 update by Aldous, 3/14/91 and 12/18/91 by Gee, 9/24/93 and 2/15/95 by Kellner, 9/3/96 by Gee [volumes 140 and 146 were overlooked in previous reviews]. P. Iyer, 10/1/97.

MBC is methyl 2-benzimidazolecarbamate, a breakdown product of several fungicides including benomyl, thiophanate-methyl, and other thiophanates.

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY ONE-LINERS

294-140 123817 "Assessment of the Mammalian Toxicity and Potential Human Health Effects of Benomyl" (Hurtt, M. E., Reynolds, V. L. and Stadler, J. C., Haskell Laboratory for Toxicology and Industrial Medicine, Du Pont, 1/93) This document reviews studies in many areas of toxicology including genotoxicity, acute toxicity, subchronic and chronic toxicity and effects on development and reproduction. It contains approximately 15 pages of citations. No worksheet. (Gee, 8/30/96)

RAT COMBINED TOXICITY/ONCOGENICITY STUDIES

NOTE: DPR considered the collective data on chronic rat feeding studies to serve the purpose of a "combined" rodent (chronic/oncogenicity) study as of 5/16/89, and no further rat chronic or oncogenicity study is required at this time. No individual study was classified as individually "acceptable", however studies 059:036267 and 079:044582, as supplemented by information requested by DPR, are considered to have addressed the basic purposes of a "combined" study.

Some major concerns which remained prior to 5/16/89 related to the test article: (1) the recognized instability of the parent compound, Benomyl, in diet; (2) the effects that formulation excipients might have on toxicity; and (3) lack of periodic analyses of test article in feed. These concerns were effectively addressed by Dr. O'Neal, in a meeting with DPR toxicologists on 4/21/88. Dr. O'Neal presented information showing that the "instability" of Benomyl was due to its hydrolysis to MBC. Modern methods of analysis, which quantitate both Benomyl and MBC, indicate that MBC is relatively stable. The excipients were examined, and none were considered likely to impact Benomyl or MBC stability. DPR noted that adequate stability of Benomyl/MBC had been shown in a more recent mouse oncogenicity study (060:036269). Thus, issues relating to test article were effectively resolved as of 4/21/89.

The other primary concern which DPR had about the rat chronic studies was lack of ophthalmology. DPR indicated in the meeting of 4/21/88 that the overall evaluation of chronic effects on the eye would be resolved by a combination of (1) multiple sections of eyes from dog chronic study 059:036268 and (2) the normal evaluations (single section per eye) of the two rat studies, 059:036267 and 079:044582. On receipt of the multiple section evaluations of eyes from dog study, 059:036268, DPR considered that the overall consideration of ophthalmology was complete for both species. At this time the rat chronic/oncogenicity data gap was considered filled (see review by J. Gee on the dog study, dated 5/16/89. (The above overview by Aldous, 12/22/89).

BENOMYL

294-059 036267 (with rebuttal in -076:043797): "Long-Term Feeding Study in Rats with 1-Butylcarbonyl-2-Benzimidazolecarbamic Acid, Methyl Ester [INT-1991; Benlate; Benomyl];" Haskell Laboratory, 8/15/69; benomyl (INT-1991, 50% or 70% AI) at 2500, 500, 100, or 0 ppm AI in the feed. Deficiencies noted: no MTD, no ophthalmoscopic exams, and instability of Benomyl in the feed. As indicated above, this study was not considered independently acceptable, however this study is considered by DPR to contribute to filling the "combined" study data requirements. (Apostolou, 11/18/85; Martz, 6/4/86; Aldous, 12/22/89; the latter review did not involve a worksheet, but this Summary was updated for clarification).

EPA One-liner: "Systemic NOEL > 2500 ppm."

NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/07/89) notes EPA classification as "Core Minimum" as a chronic study, and "Supplementary" as an oncogenicity study..

294-076 043797: Rebuttal and supplemental information to # 036267. Contains narrative comments regarding dose level selection, data about feed analysis and stability and a supplemental pathology report. Stability data indicate 50% loss in 2 days at room temperature, with only 19% of activity remaining after 5 days. Refrigerated samples retained activity for 7 days. This stability issue was considered a major problem for this study until clarified as indicated in introductory paragraphs, above. One-liner added 9/4/87, Martz; modified on 12/22/89, Aldous.

MBC

294-079 044582 (with rebuttal in -095, Tabs 3 and 4): "Long-Term Feeding Studies in Rats and Dogs With 2-Benzimidazolecarbamic Acid, Methyl Ester [INE-965] in Rats"; Haskell Laboratory, 5/25/72; MBC formulated as wettable powder, at 5000, 500, 250, 100, or 0 ppm in the feed with a fifth group starting at 2500 ppm and increased to 10,000 ppm by week 20, to CD rats; slight increase in liver weight; **Possible adverse effect** in liver: increased incidence and severity of pericholangitis/cholangiohepatitis, mainly females, with NOEL = 100 ppm. First review: UNACCEPTABLE: no MTD, no feed analysis, inadequate group sizes and no ophthalmoscopic exams. Rebuttal partially answered deficiencies (9/4/87), but report was still classified as unacceptable due to the absence of feed analysis and ophthalmoscopic exams. This study was considered to contribute to filling the "combined" rat data requirement on 5/16/89, as indicated in the introductory paragraphs, above.

REVIEW: 7/15/86 by Martz, rebuttal response and second review 9/4/87 by Martz, with NOEL change (see "COMMENT" below). Updates by Aldous, 12/22/89.

NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/07/89) notes EPA classification as "Core Minimum" for oncogenicity and chronic study data requirements.

294-095 TABS 3 and 4 (no record#): Narrative rebuttal to # 044582. Provides comments about dose level selection, frequency of clinical observations, clarification of urinalysis and information about feed analysis. Analysis of single batch of blends indicated acceptable AI content, ranging from 87%-108% of intent. Reference is made to AI/feed stability analysis data generated in a mouse oncogenicity study with MBC which DPR accepted (see #44585 in -080). This could satisfy our concern retrospectively, except that stability data were generated with technical material whereas the combined rat study utilized formulated material containing approximately 20% to 50% excipients whose effect on stability is unknown. The 9/4/87 DPR review indicated that based on this as well as on the absence of ophthalmoscopic exams, this study could not be upgraded. As indicated in the note at the beginning of this section, the collective rat chronic data now are considered to fill the "combined" study data gap. Martz, 9/4/87 (no separate Worksheet for rebuttal itself); Aldous (no worksheet), 12/22/89.

COMMENT: The MBC rat feeding study (079:044582) was originally reviewed as demonstrating an adverse effect based on an increased incidence and severity of "spontaneously-occurring cholangiohepatitis/pericholangitis" in the 10,000 and 5000 ppm groups with 500 ppm being the NOEL. Re-review of this report as part of the rebuttal process led to a reduction of the NOEL to 100 ppm, based on an increased overall lesion incidence in 500 ppm females as well as an increase in lesion severity in that group. The tabulation of lesion and severity as well as the basis for the NOEL change is covered in a separate "Supplemental Information or Peer Review Worksheet" dated 9/4/87, by F. Martz.

CHRONIC DOG STUDIES

COMMENT ON CHRONIC DOG STUDIES: The hepatotoxic potential of benomyI/MBC is well documented when all 3 studies are considered together, with the newest study demonstrating a clear NOEL of 200 ppm. The new study [1986 Haskell Labs study on MBC] also demonstrated the absence

of testicular atrophy under guideline test and husbandry conditions, so that adverse effect noted in the earlier study [1970 Haskell Labs study on Benomy] can be discounted. 9/3/87, Martz. With submission of record # 072845, reexamination of eyes from record # 036268 [1970 Haskell Labs study on Benomy], the collective data on rodent/non-rodents are upgraded to adequate. Thus, **although no single dog chronic study is independently classified as "acceptable", the data requirement for a dog chronic study is filled.** Gee, 5/16/89.

BENOMYL

294-059 036268 (with rebuttals in -076, 43800, and -095, TAB 2): "Long-Term Feeding Study in Dogs with 1-Butylcarbonyl-2-Benzimidazolecarbamic Acid, Methyl Ester [INT-1991; Benlate; Benomy];" 2 year study with 1 year interim sacrifice; Haskell Laboratory, 3/17/70; INT-1991, 50% pure with remainder as formulation excipients, at 2500, 500, 100, or 0 ppm AI in the diet to 4/sex/level with interim sacrifice of 1/sex/level at 1 year. **Possible adverse effect** in liver: increased alkaline phosphatase, SGPT and cholesterol (males mainly) with "cirrhosis" at 2500 ppm; testicular atrophy with no clear NOEL due to intercurrent disease; rebuttals partially satisfy major deficiencies, but study still UNACCEPTABLE in absence of ophthalmoscopic exams.

REVIEW: original 11/20/85 by Apostolou, rebuttal reviews 6/9/86 and 9/2/87 by Martz. See comment under 107 # 072845 below. Gee, 5/16/89.

EPA One-liner: "systemic NOEL = 500 ppm,...LEL = 2500 ppm (HDT, cirrhosis and adverse effects on testis. No effect on sperm production." NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/07/89) notes EPA classification as "Core Minimum".

294-076 043800: Rebuttal and supplemental information to # 036268. Contains comments on number of animals, study duration, feed analysis and stability as well as a supplemental pathology report discussing liver and testicular findings. Does not upgrade study. One-liner added 9/3/87, Martz.

294-095 TAB 2 (no record#): Second rebuttal to # 036268. Provides clarification of feed preparation and feeding procedures, which generally ameliorate DPR concerns about compound/feed stability. Does not upgrade study in absence of ophthalmoscopic exams. 9/2/87, Martz (no separate Worksheet).

294-107 072845 Supplement to 036268. Results of additional sections of eyes from the study as discussed at the April 21, 1988, meeting with the registrant for upgrading the total data. Supplement dated 11/14/88. A total of seven sections, about 100 microns apart, including the original section, were evaluated histologically. With this submission, with negative results, the collective data for chronic feeding studies in rodents and non-rodents is considered acceptable. Gee, 5/16/89.

MBC

294-079 044584 "Long-Term Feeding Studies in Rats and Dogs with 2-Benzimidazolecarbamic Acid, Methyl Ester [INE-965]," Haskell Laboratory, 5/25/72; 2-year study with 1 year interim sacrifice; INE-965 formulated as a wettable powder, at 2500, 1500, 500, 100, or 0 ppm AI in the feed to 4/sex/level initially; anorexia and weight loss at 2500 ppm, several dogs reduced to 1500 ppm, no effect at 500 ppm; 2 high dose males sacrificed in extremis (and replaced) in week 22, another moribund in week 42; **ADVERSE EFFECT** in liver: elevated alkaline phosphatase, SGPT, and cholesterol, decreased albumin, as well as "hepatic cirrhosis, inflammation, and fatty liver," NOEL = 100 ppm, equivalent to about 3 mg/kg/day. UNACCEPTABLE AND NOT UPGRADEABLE, no feed analysis or ophthalmoscopic eye examinations.

REVIEW: 6/14/86 with second review 11/6/86, both by Martz.

NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical

(dated 2/07/89) notes EPA classification as "Core Minimum".

294-093 049262: "One-year Feeding Study in Dogs with INE-965;" Haskell Laboratory, 6/27/86; MBC, 98.8% pure, at 500, 200, 100, or 0 ppm in the feed for 1 year to 5/sex/level; no histopathologic changes; slight increase in serum cholesterol and decrease in serum albumin at 500 ppm, not considered adverse effects by themselves; NOEL = 200 ppm, equivalent to about 7 mg/kg/day; UNACCEPTABLE - no ophthalmoscopic exams (otherwise OK); possibly upgradeable with additional information.

REVIEW: 11/4/86 by Martz.

EPA One-liner: none in Branch Library.

MOUSE ONCOGENICITY STUDIES

NOTE: Additional information provided in Document 294-117 affects interpretation of Benomyl and MBC mouse oncogenicity studies in three important ways: (1) Record 088852 contains a peer review of all available liver slides from the two studies below, which are accepted by DPR. That review team concluded that hepatocellular adenoma incidence and multiplicity was increased by Benomyl and MBC without definitive NOELs. In addition, non-neoplastic foci of cellular alteration were observed in some instances. This is a major change from original reports, which had indicated increases in hepatocellular carcinoma incidence for both Benomyl and MBC. (2) Record 088852 also contains three publications. The chief importance of these articles for this Summary is that the comparatively uncommon tumors, hepatoblastomas, were almost always found within or adjacent to hepatocellular adenomas or carcinomas. Thus hepatoblastomas should not be considered as an independent tumor type. (3) Record 088853 presents several lines of evidence that Benomyl elicits significant liver toxicity at high doses, which would be expected to predispose these animals to hepatocellular tumors. Aldous, 9/21/90.

BENOMYL

****294-060 to -062, 036269-71** Wiechman, B.E., "Long-Term Feeding Study with Methyl-1-(Butylcarbonyl)-2-Benzimidazolecarbamate, (INT-1991, Benomyl, Benlate) in Mice". Haskell Laboratory, Report No. 20-82, 1/26/82. Benomyl (INT-1991), 99% pure, at 0, 500, 1500, or 5000 ppm in the feed to CD-1 mice for 2 years [the latter group received 7500 ppm for 37 weeks before dose was reduced to 5000 ppm due to excessive toxicity]. **Possible adverse effect:** increased incidence and/or multiplicity of hepatocellular adenomas in both sexes without an apparent NOEL. High dose males and females also had increased incidence of foci of hepatocellular alteration. [See 117:088852 and associated DPR review for data on hepatocellular tumors and altered foci.] Additional non-neoplastic lesions in livers of high dose males considered to be treatment-related were noted in a 8/13/86 review by Martz. Other lesions in various tissues, possibly related to treatment, were also generally restricted to high dose males, and are noted in the same review. The rebuttal in Document 294-076 (below) was considered in the 8/13/86 review by Martz. DPR review history: Study **accepted** in 11/25/85 by Apostolou, with indication of "possible adverse effect" (liver neoplasia); re-examination by Martz on 8/13/86 confirmed acceptability and "possible adverse effects" status; re-examination by Aldous on 9/24/90 involved worksheets for supplementary data in Document 294-117 (see note above and individual 1-liners, below) noted that hepatocellular adenomas, not carcinomas, were increased in both sexes. Study status; **Acceptable, possible adverse effect**. Aldous, 9/24/90.

EPA One-liner: "Oncogenic NOEL < 500 ppm male and female significant increase in hepatocellular neoplasms in male and female." No grade given.

294-076 043798, 043799: Rebuttal asserting that the mouse hepatocellular tumors are not biologically significant [to human health]. Assertion is supported by an article, "The relevance of mouse liver hepatoma to human carcinogenic risk" [A report of The International Expert Advisory Committee to the

Nutrition Foundation, Sept. 1983]. The DPR review of 8/13/86 considered this article, but considered that the "weight of evidence" of a treatment effect of potential relevance to human health was sufficiently strong that DPR should continue to classify findings as "possible adverse effects". The elevated tumor incidence in high dose females, which do not have high background incidence of such tumors, was specifically mentioned by Martz in the 8/13/86 review.

294-117 088852 [supplementary to 294-060:036269 (mouse oncogenicity study with Benomyl) and 294-080:044585 (mouse oncogenicity study with MBC)]. Frame, S. R., and Van Pelt, C. S., "Oncogenicity studies with benomyl and MBC in mice: Supplemental peer review". Re-evaluation of liver slides for the above two studies by two Haskell Laboratory pathologists (presumably the two authors, above), together with EPL pathologist, Jerry F. Hardisty, D.V.M. Report date: 6/28/90. The re-evaluation employed NTP criteria for classifying lesions. The re-evaluation found the incidence and/or multiplicity of adenomas to be increased at one or more dose levels for both sexes following treatment with Benomyl or MBC. There was no definitive NOEL for adenomas. Unlike the original pathologist's evaluation, re-examination of slides did not confirm a treatment effect on hepatocellular carcinoma incidence. High dose males treated with Benomyl had increased incidence of foci of cellular alteration. New data are tabulated in the present review. Aldous, 9/19/90.

294-117 088852 [The first of 3 related published articles within this record, supplementary to lifetime Benomyl and MBC studies]. Nonoyama, T., Fullerton, F., Reznik, G., Bucci, T.J., and Ward, J.M. "Mouse hepatoblastomas: A histologic, ultrastructural, and immunohistochemical study". Vet. Pathol. 25:286-296 (1988). Hepatoblastomas were studied in mice with the following variables: strain (B6C3F1 and BALB/c), sex, and amount of dietary 2-acetylaminofluorene (2-AAF). There were 96/sex/group; males received 0, 20, 40, 60, or 80 ppm 2-AAF, and females received 0, 100, 125, 150, 200, or 250 ppm 2-AAF. Study duration: 2 yr. Twenty-two hepatoblastomas were found: 20 of these in the B6C3F1 mice. Hepatoblastomas were more common in males than in females, and appeared to be dose-related to 2-AAF. All but 3 of the 22 hepatoblastomas were located within or adjacent to hepatocellular adenomas or carcinomas. Morphological characteristics indicated that the hepatoblastomas were less differentiated than hepatocellular adenomas or carcinomas. Histogenesis of the hepatoblastomas could not be established, however investigators did not find evidences of transition between hepatoblastomas and other hepatocellular tumors. Aldous, 9/20/90.

294-117 088852 [The second of 3 related published articles within this record, supplementary to lifetime Benomyl and MBC studies]. Diwan, B.A., Ward, J.M., and Rice, J.M., "SHORT COMMUNICATION: Promotion of malignant 'embryonal' liver tumors by phenobarbital: increased incidence and shortened latency of hepatoblastomas in (DBA/2 X C57BL/6)F1 mice initiated with N-nitrosodiethylamine", Carcinogenesis 10:1345-1348 (1989). Male mice were used in a study in which variables were (a) strain, (b) presence or absence of initiator [N-nitrosodiethylamine (NDEA)], (c) presence or absence of promoter [phenobarbital (PB)], and (d) age to sacrifice (33 wk or 47 wk). Test animals were all hybrids of the above two strains, but groups were either offspring of DBA/2 males and C57BL/6 females (B6D2F1 mice), or of DBA/2 females and C57BL/6 males (D2B6F1 mice). Each combination of a, b, c, and d above involved 10 mice. As expected, the hepatocellular tumor yield was increased by NDEA, particularly in PB-promoted mice. The NDEA/PB mice of either strain had relatively high incidence of hepatocellular adenomas at wk 33, and of adenomas and carcinomas at wk 47. Ten mice had one or more hepatoblastomas: all of these from NDEA/PB groups, and 9 of these were D2B6F1 mice. Hepatoblastomas were generally found in or adjacent to hepatocellular adenomas or carcinomas. Investigators concluded that susceptibility to hepatoblastomas is based on an autosomal dominant trait. Aldous, 9/20/90.

294-117 088852 [The third of 3 related published articles within this record, supplementary to lifetime Benomyl and MBC studies]. Diwan, B.A., Rice, J.M., and Ward, J.M. "Strain-dependent effects of phenobarbital on liver tumor promotion in inbred mice". Prog. Clin. Biol. Res. 331:69-83 (1990). Note

from the 1-liner above that these investigators found strain differences in male mice to hepatoblastoma development, and found that initiation and promotion was required to elicit hepatoblastomas under conditions of the study. The present article summarizes a subsequent study, which confirmed the development of hepatoblastomas in D2B6F1 males, but which found no hepatoblastomas in D2B6F1 females under identical treatment. No DPR worksheet. Aldous, 9/20/90.

294-039 965471 Partial duplicate of 060:036269, above.

294-117 088853 [supplementary to 294-060:036269 (mouse oncogenicity study with Benomyl)]. Van Pelt, C. S., "28-Day feeding study with Benomyl in mice", Haskell Laboratory, 8/15/90. Benomyl (Belle Plant Lot #F60317K, 96.1%) was fed to CD-1*(ICR)BR mice. Doses of 0, 100, 500, 3750, or 7500 ppm Benomyl were administered to groups of 20 male mice: half were sacrificed at 14 days, half at 28 days. Emphasis was placed on liver toxicity: livers were evaluated for pathology, cell proliferation (BrdU incorporation), b-oxidation activity of peroxisomal fraction, and cytochrome P-450 content. Liver relative weights of 3750 and 7500 ppm groups were statistically significantly elevated at both sacrifice times, and absolute weights of both groups were statistically significantly elevated on day 14 also. Minimal to mild hypertrophy (generally centrilobular) was observed in both time periods in the two higher dose groups. Cell proliferation was suggested by non-significant elevations in BrdU uptake at 28 days in the 3750 and 7500 ppm groups. Statistically significant increases in cytochrome P-450 content were found at days 14 and 28 in 7500 ppm groups. Peroxisomal activity was apparently not affected in any groups. A provisional NOEL of 500 ppm is suggested, however additional electron micrographs will be examined for analysis of SER proliferation in liver. Data support, but do not prove, the idea that non-genotoxic mechanisms are causes of mouse liver parenchymal cell tumors. Aldous, 9/21/90.

MBC

****294-080 & 81, 044585 & 86;** "Long-Term Feeding Study with 2-Benzimidazole-carbamic Acid, Methyl Ester (MBC, INE-965) in Mice;" Haskell Laboratory, 1/26/82; MBC, 99.3% pure, at 7500, 1500, 500, or 0 ppm in the feed to CD-1 mice for 2 years; ONCOGENICITY EFFECT in liver: hepatocellular adenomas and carcinomas in females with NOEL<500 ppm (LDT); hepatotoxicity in males only with NOEL<500 ppm; report complete and study ACCEPTABLE.

REVIEW: 7/1/86 by Martz.

EPA One-liner: none in Branch Library.

294-039 965472 Summary of 080:044585, above.

294-081 044587-92: "Carcinogenicity Study with Carbendazim in Mice;" Central Institute for Nutrition and Food Research (Netherlands), 9/76; MBC, 99% pure, at 5000, 300, 100, or 0 ppm in the feed to Swiss mice for 18 months; ONCOGENICITY EFFECT in liver: at 5000 ppm, hepatocellular adenomas in females and hepatoblastomas in males; liver weight elevation in both sexes at 500 ppm; overall NOEL = 300 ppm; incomplete - summary only with additional review comments.

REVIEW: 7/16/86 by Martz.

EPA One-liner: none in Branch Library.

294-082 to -085 044593-96: "Repeated-dose (24 month) Feeding Study for Determination of the Carcinogenic Effect of HOE 17411 0 F AT204 (Carbendazim) in Mice;" Hoechst AG (Frankfurt), 10/13/82; MBC, >99% AI, at 5000, 300, 150, 50, or 0 ppm in the feed to Hoe:NMRKf(SPF71) mice for 22 months; **ADVERSE EFFECTS:** hepatotoxicity and ovarian granulosa cell tumors and/or luteomas with NOEL = 150 ppm for both effects. Acceptable, as supplement to #44587-92, with additional information.

REVIEW: 8/5/86 by Martz.

EPA One-liner: none in Branch Library.

REPRODUCTION AND FERTILITY STUDIES

BENOMYL

**** 294-124 096358** "Reproductive and Fertility Effects with DPX-T1991-529 (Benomyl) Multigeneration Reproduction Study in Rats." (Mebus, C. A., Haskell Laboratory, Report No. 765-90, 2/21/91) Benomyl, Lot # F60317K, 99%, was fed in the diet at 0, 100, 500, 3000 or 10,000 ppm to 30/sex/group CrI:CD BR rats. There were two generations with one litter in the first and two in the second. Pups were culled on day four. Parental males and females of the control and high dose groups were subjected to microscopic examination of the reproductive organs; in addition the testes and epididymides of all males were examined. Body weights were significantly lower at 10,000 ppm (nominal) for adult males and females of both the P1 and F1 generations. Pup weights were lower in the 3000 ppm in the F2A and B litters and in all litters in the 10,000 ppm groups with decreased live pups at culling at 10,000 ppm. **Possible adverse effect:** Lower sperm counts in the 3000 and 10,000 ppm males, testicular atrophy and degeneration (4/30 and 29/30 in P1 and 9/30 and 21/25 in F1 3000 and 10,000 ppm groups respectively), oligospermia in the epididymides (unilateral and bilateral with 1/30 at 3000 ppm and 26/30 at 10,000 ppm in P1, 9/30 and 20/25 in F1 respectively). NOEL = 500 ppm in males, 3000 ppm in females (decreased body weights). **Acceptable.** (Gee, 3/14/91)

294-111 73672 Protocol for Multigeneration reproduction study in rats (294-124:096358). No worksheet.

294-065 036315: "Three-Generation Reproduction Study in Rats with 1-Butylcarbamoyl-2-Benzimidazolecarbamic Acid, Methyl Ester (INT-1991);" Haskell Laboratory, 11/18/68; benomyl in wettable powder, 50% or 70% AI, at 2500, 500, 100, or 0 ppm AI in the feed to CD rats; no compound-related effects. Study UNACCEPTABLE AND NOT UPGRADEABLE, no MTD, no feed analysis (instability shown in rebuttal to benomyl combined rat study, see #43797, 076 above), inadequate group size.

REVIEW: 12/26/85 by Apostolou, second opinion 6/4/86 by Martz.

EPA One-liner: "Systemic NOEL = 100 ppm." NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/07/89) notes EPA classification as "Core Minimum".

MBC

294-077 044559 (with rebuttal in -095, TAB 4): "Long-Term Feeding Studies in Rats and Dogs with 2-Benzimidazolecarbamic Acid, Methyl Ester [INE-965];" Haskell Laboratory, 5/25/72; MBC formulated in wettable powder; 5000, 500, 100, or 0 ppm AI in the feed to CD rats with a fifth group receiving 2500 ppm increased to 10,000 ppm after 20 weeks; 3 generation, 2 litter study with F₀ rats "borrowed" from combined study; **ADVERSE EFFECT:** neonatal growth retardation @ 5000 and 10,000 ppm, NOEL = 500 ppm; no parental MTD. UNACCEPTABLE AND NOT UPGRADEABLE, no MTD.

REVIEW: 7/10/86 by Martz, rebuttal response 9/2/87 by Martz.

NOTE: The memo from EPA to DPR addressing differences in data gap status for this chemical (dated 2/07/89) notes EPA classification as "Core Minimum".

294-095, TAB 4: Rebuttal to # 044559, similar to that given for combined rat study for MTD and feed analysis. Does not upgrade study. 9/2/87, Martz (no separate Worksheet).

294-079 044583 Exact duplicate of 077:044559, above.

EXPLORATORY FERTILITY STUDIES

294-065 036317 Carter, S.D., and Laskey, J.W., "Effect of Benomyl on Reproduction in the Male Rat;" Health Effects Research Laboratory, US EPA, in Toxicology Letters 11:87-94, 1972. Benomyl (technical grade) administered for 5 consecutive days/week for 2 weeks via gavage at 0, 200, and 400 mg/kg/day in block one and at 0 and 400 mg/kg/day in block two of male Sprague-Dawley rats (4-6 animals/treatment group). **Possible adverse effects indicated:** there was a 35-48% depression in total epididymal sperm count and in the vas deferens sperm concentrations at both treatment levels 14 days after termination of treatment with benomyl. Not applicable for reproduction data requirement purposes but has useful mechanistic information. First review 11/26/85 by Apostolou, second review and Worksheet by Margolis, 8/10/87; 9/2/87, Martz.

294-065 036316 Carter, S.D., "Effect of Benomyl on the reproductive development in the prepubertal male rat". [manuscript to be submitted to J. Toxicol. Environ. Health] [from 1982 Thesis]. 33-day old Sprague-Dawley rats were given 10 daily gavage treatments with 0 or 200 mg/kg/day Benomyl, and then killed at intervals of 3 to 59 days after cessation of dosing. There were no changes in sperm concentration in the vas deferens, in total epididymal sperm, nor were there changes in testicular histology. **No adverse effects indicated. Unacceptable.** Aldous (no worksheet), 9/27/90.

294-104 067403 Carter, S.D., Hess, R.A., and Laskey, J.W., "The Fungicide Methyl 2 Benzimidazole Carbamate Causes Infertility in Male Sprague-Dawley Rats." Biology of Reproduction 37:709-717 (1987). (Health Effects Research Laboratory, U.S. EPA, Research Triangle Park). MBC (carbendazim), 98.1% and 1.9% inerts; given by oral gavage in corn oil (2 ml/kg) at 0 or 400 mg/kg/day to male Charles River rats for 10 days. These proven males (23 - 24 per group) were 90 days of age at treatment initiation. Each male was placed with 1 female for 1 week on day 3 of treatment. Females were replaced weekly with nulliparous females for 32 weeks after termination of treatment. All males were killed at week 35 post exposure, and testicular tissues were examined. Females were killed 12 days after breeding period, and uterine contents were examined. At termination, testicular weights in treated males were 39% lower than controls. In totally infertile males, this value was a 58% reduction. 10/24 males in the treated group failed to produce a pregnant female in the first week post treatment. By the 5th week, 16 males were infertile, and 12 remained infertile throughout the study. Pathology showed atrophic seminiferous tubules lined by Sertoli cells, but displaying very limited spermatogenesis, with 7/24 showing 100% tubule atrophy. **Not acceptable, due to study design**, but useful supplemental data demonstrating "**possible adverse effects**". Gee, 6/13/88.

294-104 067404 Carter, S.D., Hein, J.F., Rehnberg, G.L., and Laskey, J.W. "Effect of Benomyl on the Reproductive Development of Male Rats." J. Toxicol. Environ. Health 13:53-68 (1984). (Health Effects Research Laboratory, U. S. EPA, Research Triangle Park). Benomyl, technical grade, no purity stated. Experiment 1: 33-day old males were given 10 daily doses by gavage at 0 or 200 mg/kg/day; after 3, 17, 31, 45 and 59 days post treatment, 8 males per group were sacrificed for gonadal tissue examinations. Experiment 2: 33, 54 and 75- day old rats [representing prepubertal, pubertal, and postpubertal ages, respectively] were given 0, 125, 250, 500 or 1000 mg/kg/day (5/interval/dose) for 5 days divided into two dosings/day. Blood samples were taken at 29 days after treatment and animals were sacrificed 31 days after treatment. Results of Expt. 1: no effect on weights of testes, seminal vesicles, or epididymides (caput or cauda), on sperm counts or on time of appearance of spermatozoa in treated group. Expt. 2: no significant effects were seen in prepubertal animals; epididymal sperm counts were depressed in pubertal animals; and postpubertal animals showed a wide variation in susceptibility of sperm counts. Histological exams of testicular tissue showed an increased incidence of diffuse hypospermatocytogenesis in pubertal and postpubertal males. **Unacceptable, not upgradeable** due to study design, with useful supplementary data showing a **possible adverse effect**. Gee, 6/13/88.

294-104 067405 Dashiell, O.L., "Ten-Dose Oral Subacute Test with Reproduction Study." (Haskell Laboratory, 3/10/78, Report 121-78). Benomyl, 50% with 50% inerts; given by gavage in corn oil at 0 or 200 mg/kg/day for 10 doses to young adult male ChR-CD rats, 30 per group. 5/group were each mated with 2 females 3 days after the last dose. The same males were mated a second time 59 days after the last dose. The number of pregnancies in the first mating was 9/10 for controls and 3/10 for treated group. In the second mating, the numbers were 9/10 and 10/10 respectively - no other reported parameters were affected. In addition, control and treated males, 5 per group, were sacrificed at 4 hours, 14, 28, 42, 70 and 90 days after the last dose and the testes and epididymides were examined. Testicular weights were reduced, and microscopic lesions were focal to diffuse degeneration of germinal epithelium, accompanied by giant cells, occasional sperm granulomas, and reduction or absence of sperm. Some effects were still seen at 90 days recovery. **Unacceptable, not upgradeable** due to study design, with useful supplementary data showing a **possible adverse effect**. Gee, 6/16/88.

RAT TERATOLOGY STUDIES

BENOMYL

****294-065 036320:** Staples, R.E., "Benomyl: Teratogenicity in the Rat After Administration by Gavage;" Haskell Laboratory, 9/18/80. Benomyl, 99.2% pure; 125, 62.5, 30, 10, 3, or 0 mg/kg/day by oral gavage to CD rats. **Possible adverse effects:** decreased litter size and fetal weights, microphthalmia or anophthalmia, and hydrocephaly. NOEL = 3 mg/kg/day (microphthalmia); maternal NOEL = 125 mg/kg/day. Report complete and study acceptable in conjunction with # 036323 below. Martz, 6/11/86.

EPA One-liner: "Unilateral microphthalmia at 10 mg/kg/day (2 animals), NOEL = 30 mg/kg/day, LEL = 62.5 mg/kg (embryotoxicity)." No grade given.

****294-065 036323:** Staples, R.E., "Benomyl Gavage: Teratogenicity in the Rat", Haskell Laboratory, 10/1/82. Benomyl, 99.1% pure; 62.5, 30, 20, 10, 6.25, 3, or 0 mg/kg/day by oral gavage to CD rats. **Possible adverse effects:** decreased fetal weights, microphthalmia and hydrocephaly at 62.5 mg/kg only. Study is valid and results support change of previous NOEL from 3 to 30 mg/kg/day. Report complete and acceptable as supplement to # 036320 above. Martz, 7/7/86.

EPA One-liner: "NOEL = 30 mg/kg, LEL = 62.5 mg/kg (microphthalmia)." Graded as "supplementary; upgraded to minimum."

COMMENT: Neither # 036320 nor # 036323 is independently acceptable. The former lacked dosing solution analysis, but this deficiency was corrected by analytical results in the latter study. The latter was unacceptable by itself because only heads were examined, in order to clarify craniofacial malformations noted in the former. However, both were excellent studies and complemented each other. They are both acceptable when taken together, and fill the data requirement. Note also that the latter study supports a change of the NOEL from 3 mg/kg to 30 mg/kg. Comment added 9/16/87, Martz.

294-065 036319 (with rebuttal in -076, 43804): "Teratogenic Study in Rats With 1-Butylcarbamoyl-2-Benzimidazolecarbamoyl Acid, Methyl Ester (INT-1991; Benlate; Benomyl);" Haskell Laboratory, 7/9/70; benomyl formulated as wettable powder, 50% AI at 5000, 2500, 500, 100, or 0 ppm in the feed to CD rats. No maternal or fetal effects. Original status was unacceptable but possibly upgradeable. Rebuttal cannot upgrade study, still UNACCEPTABLE but not upgradeable.

REVIEW: original 12/2/85 by Apostolou, rebuttal 6/15/86 by Martz.

EPA One-liner: "Terato NOEL = 5000 ppm (HDT)," with no grade given.

294-076 043804: Rebuttal to # 036319. Narrative explanation of randomization, dam necropsy observations, absence of corpora lutea counts, absence of soft tissue examination at lower dose levels,

and dose level justification. While the latter could satisfy the MTD criticism, documented AI instability in the feed (see # 043797, -076 above) renders study not upgradeable. One-liner added 9/8/87, Martz.

294-065 036324 Kavlock, R.J., Chernoff, N., Gray, L.E. Jr., Gray J.A., Whitehouse, D., "Teratogenic effects of Benomyl in the Wistar rat and CD-1 mouse, with emphasis on the route of administration", Toxicol. Appl. Pharmacol. 62:44-54 (1982). A rat and mouse study, with rat exposure via gavage or in diet. Only gavage portion of rat study is relevant, due to the high NOEL of the dietary segment. Rats were treated with 0, 15.6, 31.2, 62.5, or 125 mg/kg/day Benomyl (tech., in 1 ml corn oil/rat/day) days 6-15. Maternal toxicity was not apparent. NOEL for developmental toxicity = 31.2 mg/kg/day (dose-related reduction in fetal weight, hydrocephaly, microphthalmia, fused ribs, fused vertebrae, and decreased ossification in tail and in vertebral centra). Findings at the HDT of 125 mg/kg/day included: full litter resorptions in 6 of 11 surviving pregnant dams, enlarged lateral ventricles, enlarged renal pelves, and delayed ossification (more widespread than at 62.5 mg/kg/day). Fetotoxicity and teratogenicity findings in absence of obvious maternal toxicity indicate **possible adverse effects**. Note that similar findings were noted in records 036320 and 036323 in this volume. Since the latter studies identified a NOEL for developmental toxicity, it is unlikely that this study will be required for risk assessment. **Unacceptable, upgrade unlikely**. Apostolou, 12/3/85 (brief review): one-liner by Aldous, 9/25/90 (no written review).

294-039 965482 (duplicate of records 036324 (above) and 036325 (below)).

MBC

294-077 044558 (With rebuttal and supplemental information in -095, TAB 5 and 051508): "Teratogenicity Study in Rats with 2-Benzimidazolecarbamic Acid, Methyl Ester (INE-965);" Haskell Laboratory, 11/3/70; MBC with excipients, 53% AI as formulation; administered to CD rats at 10000, 7500, 5000, 2500, 500, 100, or 0 ppm AI in the feed. No effects on any parameters. **UNACCEPTABLE** and not upgradeable - inadequate dose levels, no maternal toxicity, no feed analysis, effects of formulation excipients on a.i. absorption unknown.

REVIEW: Martz, 7/8/86, with second review and rebuttal response, Margolis, 7/31/87.

EPA One-liner: none in Branch Library.

294-095 051508 [TAB 5]: Narrative rebuttal and supplemental information to # 044558 above regarding MTD. Argument doesn't fully answer concerns and can not upgrade study. 9/8/87, Martz (no separate Worksheet).

294-065 036326 Delatour, P., and Richard, Y. "Embryotoxic and antimetabolic properties of benzimidazole compounds". Therapie 31:505-515 (1976). Several benzimidazole-related compounds were tested for developmental toxicity, and for *in vitro* and *in vivo* antimetabolic activity. A few SD rats were treated orally (a total of 13 dams divided between 3 dosages between 9.6 and 38 mg/kg/day for MBC, 7 dams at 116 mg/kg/day for benomyl) for a limited teratology study. Benomyl was apparently inactive, but MBC was inactive at 9.6 mg/kg/day, caused 72% embryoletality and 100% "external anomalies" among survivors at 19 mg/kg/day, and 100% embryoletality at 38 mg/kg/day. The anomalies were not quantified, however exencephaly was noted as "common" for MBC, and malformations noted as common for the more active of the series of compounds included "exencephaly, meningocele, hydrocephaly, hare lip, micro-anophthalmia, hypodysplasia of the limbs, ectrodactylia, micro-anurous". **Unacceptable, not upgradeable** (due to limitations of study design), useful for general perspective of developmental toxicity of a chemical series. Aldous, (no worksheet) 9/26/90.

294-039 965483 Comments by L.W. Smith, who suggested that teratology studies for Benomyl should be by dietary rather than gavage exposure, to be relevant to human exposure situation. Gavage administration of Benomyl or MBC can be expected to elicit developmental effects by overwhelming the

organism, which is capable of tolerating comparably large doses if administered in the diet. No DPR review worksheet. "One-liner" by Aldous, 9/26/90.

RABBIT TERATOLOGY STUDIES BENOMYL

294-065 036318: "Segment II - Teratology Study -Rabbits. Fungicide 1991 (MRO-1079);" Hazleton, 7/15/68; "Fungicide 1991", 50% benomyl, at 500, 100, or 0 ppm AI in the feed to NZW rabbits, days 8-16 (insemination=day 0); rib defects at 500 ppm, probably incidental; no other fetal or maternal effects; UNACCEPTABLE AND NOT UPGRADEABLE, no MTD, no feed analysis (AI instability in feed?), inadequate group size, insufficient skeletal exams.

REVIEW: original 12/3/85 by Apostolou, second opinion 7/7/86 by Martz.

EPA One-liner: "Terata NOEL = 500 ppm (HDT)." No grade given.

294-076 043805 Rebuttal comments to 065:036318, above. Comments were considered in 7/7/86 re-review by Martz.

MBC

****294-086 045741:** "Developmental Toxicity Study of H-15647 Administered via Gavage to New Zealand White Rabbits;" Argus Research Laboratories, 7/3/85; MBC ("H-15647"), 98.7% pure; 125, 20, 10, or 0 mg/kg once daily by oral gavage to 16-18 pregnant/level, days 7-19 (insemination day = 0); **ADVERSE EFFECTS:** maternal - weight loss, decreased feed consumption, and abortion at 125 mg/kg; malformations - rib and vertebral at 125 mg/kg; embryotoxicity - total litter resorption at 125 and 20 mg/kg, reduced litter size and increased postimplantation loss, 125, 20, and 10 mg/kg. **MATERNAL AND TERATOGENIC NOEL = 20 MG/KG, EMBRYOTOXIC NOEL < 10 mg/kg (LDT);** Report complete and study ACCEPTABLE.

REVIEW: 7/9/86 by Martz (one-liner revision 9/3/87).

The data were re-reviewed and evaluation of the developmental effects of MBC was conducted using the litter (not fetus) as the unit. MBC appears to cause significant effects (postimplantation loss) at the mid and high dose level. The study remains acceptable. **Developmental NOEL = 10 mg/kg/day.** P. Iyer, 10/1/97.

EPA One-liner: none in Branch Library.

MOUSE TERATOLOGY STUDIES

294-065 036325 Kavlock, R.J., Chernoff, N., Gray, L.E. Jr., Gray J.A., Whitehouse, D., "Teratogenic effects of Benomyl in the Wistar rat and CD-1 mouse, with emphasis on the route of administration", Toxicol. Appl. Pharmacol. 62:44-54 (1982). [The same study is under Record No. 036324 for rat data]. Benomyl (tech., in 0.1 ml corn oil/mouse/day) days 6-16 to mice at 0, 50, 100, or 200 mg/kg/day. There was no apparent maternal toxicity. Developmental effects NOEL = 50 mg/kg/day (based on fetal weight decrements, delayed ossification in vertebral centra, increased supernumerary ribs, enlarged renal pelvis; and the anomalies: cleft palate, hydronephrosis, fused ribs, fused vertebrae, and short and/or kinky tail). The above findings, at 100 mg/kg/day, were generally more markedly manifest at 200 mg/kg/day. Additional findings at 200 mg/kg/day were increased fetal mortality, enlarged lateral ventricles, hydrocephaly, micrognathia, polydactyly, oligodactyly, and umbilical hernia. Developmental findings are **possible adverse effects**, however the apparent NOEL for developmental toxicity is higher than that for rats or rabbits, therefore usefulness of these data for risk assessment is doubtful. Study is **unacceptable, and unlikely upgradeable.** Brief review by Apostolou, 12/3/85; one-liner (no

worksheet) by Aldous, 9/25/90.

GENETIC TOXICITY

294-129 111296 "Assessment of the Genetic Toxicological Studies on Benomyl and Carbendazim: A Review." (Sarrif, A. M., Haskell Laboratory for Toxicology and Industrial Medicine, du Pont, 1/31/91) The document reviews numerous reports on a number of endpoints for somatic cell and germ cell genetic toxicity. Most are given a one paragraph summary and a brief assessment of the significance of the findings. No worksheet. Gee, 12/18/91.

294-140 123816 "A Review of the Genetic Toxicity Studies on Benomyl and Carbendazim" (Reynolds, V. L. and A. M. Sarrif, Haskell Laboratory for Toxicology and Industrial Medicine, Du Pont, HLR 1-93, 1/93) The document reviews numerous studies in different species using a tier approach. Tier I consists of studies with somatic cells and Tier II, studies with germ cells. The authors concluded that benomyl and its major metabolite, carbendazim (MBC), cause specific effects resulting in aneuploidy. This was thought not to be the result of direct interaction with DNA but with other targets, for example, tubulin. Positive results for gene mutation and structural aberrations were attributed to cytotoxicity at high concentrations. The authors considered benomyl to be negative for the induction of DNA damage and repair. They proposed that the causal event of aneuploidy has a threshold. The review contains about 15 pages of citations. No worksheet. (Gee, 8/30/96)

GENE MUTATION

BENOMYL

**294-039 965485: "Mutagenicity Evaluation in Salmonella Typhimurium;" Haskell Laboratory, 8/26/81; benomyl, 99.2% pure; strains TA1535, TA1537, TA98, and TA100 (with or without rat or mouse liver S9 activation); 1000, 500, 375, 250, 100, 50, 10, 5, or 0 ug/plate. Cytotoxicity above 250, no mutagenic activity. Study ACCEPTABLE.

REVIEW: 5/9/85 by Wong.

EPA One-liner: "Not mutagenic in TA1537, 1538, 98, or 100 up to dosage levels of 250 µg/plate."

**294-076 043811 & -12 (revised report of -063, 36279): "Mutagenicity Evaluation in Salmonella Typhimurium;" Haskell Laboratory, 3/18/83 with revision 4/3/86; benomyl, 99% pure; strains TA1535, TA1537, TA98 and TA100 with or without rat liver S9 activation; 0, 10, 25, 50, 100, or 200 µg plate without S9; 0, 25, 50, 100, 250, or 500 µg/plate with S9; in duplicate, 2 trials. No evidence of increased reversion rate. Revised report complete and ACCEPTABLE.

REVIEW: original 12/5/85, rebuttal 6/17/86, both by (Remsen) Gee.

EPA One-liner: none in Branch Library.

**294-076 043809 & -10 (revised report of -063, 036278): "Mutagenicity Evaluation in Salmonella Typhimurium;" Haskell Laboratory, 3/18/83 with revision 4/7/86; benomyl, 99% pure; strains TA1535, TA1537, TA98 AND TA100 ± rat liver S9 activation; 0, 25, 50, 100, 250, or 500 µg plate, duplicate plates, 2 trials; cytotoxicity with TA1535 at 500 µg without S9 and at 1000 µg with S9. No increase in reversion rate reported. Revised report ACCEPTABLE with variances.

REVIEW: original 12/5/85, rebuttal 6/17/86, both by (Remsen) Gee.

EPA One-liner: none in Branch Library.

MBC

294-078 044572: "Mutagenicity Testing on Fungicide 1991 Metabolite (MBC) in Microbial Systems;" Institute of Environmental Toxicology (Japan), 10/17/77; MBC, 99% pure; TA1535, TA1537, TA1538, TA98, and TA100 \pm rat liver activation, 1 trial in duplicate; 0, 10, 50, 100, 500, 1000, or 3000 μ g/plate; results negative, study UNACCEPTABLE.

REVIEW: 6/18/86 by (Remsen) Gee.

EPA One-liner: none in Branch Library.

****294-095 051507, TAB 6 (revised version of 44567 in -078):** "Mutagenicity Evaluation of 2-Benzimidazolecarbamic Acid, Methyl Ester in Salmonella typhimurium." Haskell Laboratory, 10/14/77, revised 11/3/86. MBC, 99.1% or 99.3% (two analyses). 5 tester strains \pm rat liver activation; 0, 200, 400, 600, 800, 1000, 4000, 8000, or 10000 μ g/plate. **POSITIVE**, concentration dependent response with S9 in TA1537, TA1538, and TA98 (frame shift) with revertant frequency > 2X background at \geq 4000 μ g/plate for all 3 strains. TA100 significant at 4000-8000 μ g/plate, but frequencies < 2X background. Originally unacceptable but upgraded to **ACCEPTABLE** by revised report.

REVIEW: First 6/17/86 by (Remsen) Gee, re-issued version by Margolis, 7/30/87 and Martz, 9/2/87.

EPA One-liner: none in Branch Library.

****294-039 965486:** "Mutagenicity Evaluation in Salmonella Typhimurium;" Haskell Laboratory, 7/31/81; MBC, 99.6% pure; strains TA1535, TA1537, TA98, and TA100, with or without mouse or rat liver S9; 10000, 5000, 1000, 500, 100, or 0 μ g/plate. **POSITIVE** response (significant and >2X background) in TA1537 and TA98 with either rat or mouse S9 \geq 5000 μ g/plate with trend at 1000 μ g/plate; equivocal effect (concentration dependent but < 2X background) in TA100 with S9 and TA1537 without S9. Study ACCEPTABLE.

REVIEW: 5/9/85 by Wong and 9/16/87 by Martz.

EPA One-liner: none in Branch Library.

****294-078 044568:** "Mutagenicity Evaluation in Salmonella Typhimurium;" Haskell Laboratory, 6/1/83; MBC (INE-965), 99% pure; TA1537, TA1537, TA98, and TA100 \pm rat liver S9; 0, 100, 500, 1000, 5000, or 10000 μ g/plate; no increased reversion rate; no cytotoxicity at 10000 μ g/plate; study ACCEPTABLE with minor variances.

REVIEW: 6/18/86 by (Remsen) Gee.

EPA One-liner: none in Branch Library.

****294-078 044569:** "Mutagenicity Evaluation in Salmonella;" Haskell Laboratory, 9/22/83; MBC, 99% pure (Z08844); TA1535, TA97, TA98, and TA100 \pm rat liver activation; 0, 100, 500, 1000, 2500, or 5000 μ g/plate; no evidence of increased reversion rate in two trials; study ACCEPTABLE.

REVIEW: 6/18/86 by (Remsen) Gee.

EPA One-liner: none in Branch Library.

****294-078 044570:** "Mutagenicity Evaluation in Salmonella Typhimurium;" Haskell Laboratory, 9/22/83; MBC, 99% pure (Z08652); TA1535, TA97, TA98, and TA100 \pm rat liver activation; 0, 100, 500, 1000, 2500, or 5000 μ g/plate; no evidence of cytotoxicity at 10000 μ g/plate; no increase in reversion rate; study ACCEPTABLE.

REVIEW: 6/18/86 by (Remsen) Gee.

EPA One-liner: none in Branch Library.

****294-078 044574:** "Chinese Hamster Ovary Cell Assay for Mutagenicity;" Haskell Laboratory, 9/5/80; MBC, >99% pure; \pm rat liver activation, 0 to 628 μ M concentration duplicate cultures, 4 trials without S9, 3 trials with S9; concentrations changed with trials; precipitation at > 262 μ M which caused toxicity

problems; no evidence of mutagenicity; report refers to MBC as a spindle poison; study ACCEPTABLE.
REVIEW: 6/18/86 by (Remsen) Gee.
EPA One-liner: "Not mutagenic with or without metabolic activation at HGPRT locus."

****294-078 044577 (With rebuttal in -095, TAB 9):** "An Evaluation of Mutagenic Potential of MBC Employing the L5178Y TK+/- Mouse Lymphoma Assay;" SRI International, 12/80; MBC, 99% pure; L51784 TK+/- \pm rat liver S9 (F344); trial 1 @ 0-1000 $\mu\text{g/ml}$ \pm S9 with precipitation at 80 $\mu\text{g/ml}$, trial 2 @ 0-25 $\mu\text{g/ml}$ with S9, 0-100 $\mu\text{g/ml}$ without S9; **POSITIVE** mutagenic effect (frequency >2X background) at 50 $\mu\text{g/ml}$ without S9, at 12 $\mu\text{g/ml}$ with S9; originally unacceptable (AI not identified) but upgraded to ACCEPTABLE by rebuttal in -095 TAB 9.

REVIEW: Original 6/18/86 by (Remsen) Gee, rebuttal 9/9/87 by Martz.

EPA One-liner: "Dose related increase in mutation frequency at TK locus of L5178Y cells, in vitro."
(Listed with benomyl one-liners)

294-095 TAB 9: Narrative rebuttal to #44577 identifying MBC as test article, upgrades study to acceptable. 9/9/87, Martz.

****294-078, 044578:** "L5178Y Mouse Lymphoma Cell Assay for Mutagenicity;" Haskell Laboratory, 7/12/83; MBC, >99% pure; L51784 TK +/- \pm rat liver S9 (CD); 0, 25, 50, 100, 150, or 200 μM (plus other intermediate concentrations); 2 trials; no increase in mutation frequency reported; study ACCEPTABLE.

REVIEW: 6/18/86 by (Remsen) Gee.

EPA One-liner: none in Branch Library.

5-hydroxy MBC

****294-076 043813 & -14** (revised report of -063, 36280): "Mutagenic Activity of 2-Benzimidazolecarbamic Acid, 5-Hydroxy-, Methyl in the Salmonella/Microsome Assay;" Haskell Laboratory, 10/14/77, revised 4/7/86; 5-hydroxy MBC, purity 95%; strains TA1535, TA1537, TA1538, TA98, and TA100 \pm rat liver S9 activation; 0-16000 $\mu\text{g/plate}$ without S9, 0-20000 $\mu\text{g/plate}$ with S9, duplicate plates, 5 trials with increasing concentrations in each. No increase in reversion rate reported. Revised report complete and ACCEPTABLE.

REVIEW: original 12/5/85, rebuttal 6/17/86, both by (Remsen) Gee.

EPA One-liner: none in Branch Library.

COMMENT: In view of the conflicting results in numerous valid studies, the test article must be assumed to have mutagenic activity. In bacterial tests from the same laboratory, MBC caused increased reversion frequencies in strains TA1537 and TA98 with rat liver activation in 2 of 5 studies, whereas negative results were obtained in the same tester strains in 3 other studies at similar MBC concentrations. To further confuse interpretation, similar methods as well as identical rat strains for activation systems were used in all 5 studies. Due to the differences in report dates, it can be assumed that different lots of test material were used. Therefore, the participation of impurities in the mutagenic process is open to question.

Opposite results also were noted in 2 mammalian cell tests from different laboratories using overlapping test article concentrations. In the mouse lymphoma assay, SRI reported positive results with activation at 12 $\mu\text{g/ml}$, which is equivalent to about 63uM. In contrast, the same test at Haskell Laboratory was negative with activation at concentrations up to 200uM, equivalent to about 38 $\mu\text{g/ml}$. Differing activation sources were used in each study, however. SRI used S9 liver preparations from F344 male rats whereas the S9 fractions used at Haskell Laboratory were obtained from CD (Sprague-Dawley descended) males. Although the mechanism is speculative, qualitative or quantitative metabolic pathway differences between the 2 rat strains could account for the opposite mutagenicity results. Alternatively, the use of different batches of test material (containing differing impurities) could

possibly account for this discrepancy.

The registrant has advocated the latter but provided no analytical data or side-by-side assays to support that contention (see rebuttal to #44577 in TAB 9 of -095). Although that speculation is probable, it does not ameliorate concern about mutagenic activity of benomyl/MBC. Assuming that technical grade material contains similar mutagenic impurities, the manufactured pesticidal products would present mutagenic hazards regardless of the etiologic agent(s) involved. Consequently, an adverse effect status must be assigned regardless of the underlying cause. Gee, 1987.

GENE MUTATION: ADDITIONAL INFORMATION (ESPECIALLY PUBLICATIONS):

NOTE: The following studies were not included in previous Summaries of Toxicology Data, and these reports generally received only brief DPR reviews (in a few cases, no DPR worksheets had been generated). Aldous, 10/4/90.

294-064 036298 Kappas, A., Green, M.H.L., Bridges, B.A., Rogers, A.M., and Muriel, W.J., "Benomyl - A novel type of base analogue mutagen?". Mutation Research 40:379-382 (1976). Benlate (50% Benomyl a.i.) was administered at Benomyl concentrations of 0.125 to 5.0 µg/ml (slightly higher upper range for some test systems) for systems: E. coli strains WP2uvrA, WP2, CM611, Salmonella typhimurium TA1535 and TA1538. A simplified fluctuation test was used. Two assays were positive, WP2uvrA, and TA1535, both in the range of 0.125 to 1.0 µg/ml Benomyl. **Possible adverse effect indicated. Unacceptable** due to limitations in study design. de Vlaming/Apostolou, 12/3/85.

294-064 036299 Kappas, A., and Bridges, B.A. "Induction of point mutations by Benomyl in DNA-repair-deficient Aspergillus nidulans". Mutation Res. 91:115-118 (1981). Benomyl (0.25 to 0.40 µg/ml) induced reverse mutations from both biotin and pyridoxine requirement in the excision-deficient UT517 strain of Aspergillus nidulans, whereas there was no detectable mutagenic effect in the repair-proficient UT439. Benomyl (0.25 to 0.40 µg/ml) induced reverse mutations from adenine requirement in a UV-sensitive strain (UT540) of Aspergillus nidulans. **Possible adverse effect indicated. Unacceptable** due to limitations in study design. de Vlaming/Apostolou, 12/3/85.

294-064 036300 Dassenoy, B., and Meyer, J.A. "Mutagenic effect of Benomyl on Fusarium oxysporum". Mutation Res. 21:119-120 (1973). (Text without tables). Benomyl caused forward mutations, creating monoauxotrophs with several amino acid requirements. **Possible adverse effect indicated. Unacceptable** due to limitations in study design. de Vlaming/Apostolou, 12/3/85.

294-064 036301 Hastie, A.C. "Benlate-induced instability of Aspergillus diploids". Nature 226:771 (1970). Heterozygous diploid strains were distinguishable by colors (white and yellow) of the colonies. Benomyl, 0.25 or 0.5 ppm, caused increased segregation of colonies, and many of the colonies were haploid. **Possible adverse effect indicated. Unacceptable** due to limitations in study design. de Vlaming/Apostolou, 12/3/85.

294-064 036302 Bignami, M., Aulicino, F., Velcich, A., Carere, A., and Morpurgo, G. "Mutagenic and recombinogenic action of pesticides in Aspergillus nidulans". Mutation Res. 46:395-402 (1977). Benomyl (500 µg per 3 cm x 5 cm filter paper triangle) was tested for ability to induce point mutations to 8-azaguanine resistance in Aspergillus nidulans. This compound did not increase mutation frequency. **Unacceptable** due to limitations in study design. de Vlaming/Apostolou, 12/3/85.

294-064 036304 Carere, A., Ortali, V.A., Cardamone, G., Torracca, A.M., Raschetti, R. "Microbiological mutagenicity studies of pesticides in vitro". Mutation Res. 57:277-286 (1978). Benomyl (at 20 or 500 µg/3 cm x 2 cm triangular absorbent paper) was not mutagenic in the TA1535, TA1536, TA1537, or

TA1538 strains of S. typhimurium in a reverse mutation spot test with and without activation with phenobarbital-induced male rat liver. **Unacceptable** due to limitations in study design. de Vlaming/Apostolou, 12/3/85; updated by Gee, 10/1/90.

294-064 036310 Fiscor, G., Bordas, S., and Stewart, S.J. "Mutagenicity testing of Benomyl, methyl-2-benzimidazole carbamate [MBC], streptozotocin and N-methyl-N'-nitro-N-nitrosoguanidine in Salmonella typhimurium in vitro and in rodent host-mediated assays". Mutation Res. 51:151-164 (1978). Benomyl and two of its commercial preparations were tested in various gene mutation assays. These compounds were negative in in vitro spot tests, in microsomal plate assay, in liquid-culture treatments, and in the rodent host-mediated assay. The base-pair substitution S. typhimurium mutant hisG46 and the hisG46-bearing uvrB excision-repair deficient mutants TA100, TA1530, TA1535, or TA1950 were used as test organisms. At the dose levels used, benomyl was not mutagenic. MBC was tested in some of the above systems, and was also negative for mutagenicity. **Unacceptable** due to limitations in study design. de Vlaming/Apostolou, 12/4/85.

294-041 and -063 965489 Russell, J.F., Jr. "Mutagenic activity of 2-benzimidazolecarbamic acid, 1-(butylcarbamoil)-, methyl ester in the Salmonella/microsome assay". Haskell Lab Report No. 819-77, dated 10/14/77. Test article was Benlate* (50% wettable powder). Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100 were tested at concentrations of the formulation up to 1200 µg/plate in the absence of S9 or up to 750 µg/plate in presence of S9. There were two replicates per dose level in two separate experiments. Report indicates that treatments included a "slightly toxic" range (>50% of control survival: data not provided). **No adverse effect indicated**: all strains were negative with and without S9. **Unacceptable** due to choice of test article, but useful information. Aldous, 10/1/90 (no DPR worksheet).

294-041 and -063 024912 Russell, J.F., Jr. "Mutagenic activity of 2-benzimidazolecarbamic acid, 1-(butylcarbamoil)-, methyl ester in the Salmonella/microsome assay". Haskell Lab Report No. 18-78, dated 1/20/78. Test article was Benomyl, 99.05 to 99.4% purity. Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100 were tested at concentrations of the formulation up to 500 µg/plate in the presence or absence of S9. There were two replicates per dose level in up to 8 separate trials per strain/treatment/S9 combination. Evidence of toxicity was extremely variable between strains and between trials. In most cases, some toxicity was observed in several dose levels in tests without S9 activation. Strain 1537 without S9 had elevated numbers of revertants in several trials and at several dose levels. For this reason, test article was considered to be mutagenic in that strain in the absence of an activation system. This is a **"possible adverse effect"**. **Unacceptable**: Excessive variability in toxicity suggests problems in execution of study. (Upgradeability is not an issue, since later studies have been accepted.) A brief DPR review was written by J. Wong on 5/10/85. This 1-liner is by Aldous, 10/1/90 (no new DPR worksheet).

294-041 and -063 965490 Shirasu, Y., Moriya, M., and Kato, K., "Mutagenicity testing on Fungicide 1991 in microbial systems". Institute of Environmental Toxicology, Tokyo, 1/23/78. Benomyl, 99%, was tested in several systems, primarily to detect gene mutations. Tests included "Ames" test with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100; also reverse mutation test in Escherichia coli WP2 hcr. A host-mediated assay was done using Salmonella typhimurium strain G46 in mice. In addition, a DNA damage/repair study was performed: a rec-assay in Bacillus subtilis strains M45 and H-17. All results were negative. These studies were classified as **unacceptable** by J. Wong on 5/10/85, based on the following deficiencies: dosage ranges were not justified, there were no analyses of dosing solutions, there was no QA/GLP statement, and there were insufficient individual data for independent analyses. One liner by Aldous, 10/2/90.

294-041 965491, 038196, and 038197 (for host-mediated assay, rec-assay, and "Ames"-style plate tests, respectively). Shirasu, Y., Moriya, M., and Kato, K.; "Mutagenicity testing on Fungicide 1991

metabolite (MBC) in microbial systems". Institute of Environmental Toxicology, Tokyo, 10/17/77. MBC, 99%, was tested in the same systems as reported for Benomyl, above (294-041 and -063 965490). All results were negative. These studies were classified as **unacceptable** by J. Wong on 5/10/85, based on the same deficiencies listed in the cited 1-liner (above). One-liner by Aldous, 10/2/90.

294-063 036287 Lamb, M.J., and Lilly, L.J. "An investigation of some genetic toxicological effects on the fungicide Benomyl". *Toxicology* 17:83-95 (1980). [see also DPR review of the chromosomal effects portions of this report, under Record Nos. 036288 and 036289]. Either 1 mg/ml Benlate* (powdered formulation which is 50% Benomyl) or 0.5 mg/ml MBC was dissolved in 0.5% DMSO. Benomyl and MBC were fine suspensions at these concentrations. Food and water were retained from adult male *D. melanogaster* [Oregon-R strain] flies for 16 hr, then flies were placed in the presence of a drop of Benomyl, MBC, or DMSO vehicle. Differences in weights of groups of 5 flies were taken as estimates of consumption. Neither Benomyl nor MBC increased the numbers of recessive lethals significantly (even though an unusually low zero incidence in controls was obtained). Significant increases in numbers of sterile males were noted at a time period corresponding to exposure to predominantly pre-meiotic spermatocytes and spermatogonial cells for both Benomyl and MBC. The increase in sterile males was considered a **possible adverse effect** in the 12/6/85 review. It should be noted that no increases in male sterility were noted in $yw^+B/B^S Y y^+$ males used in chromosome loss and breakage tests in the same report. Original DPR review by Remsen (Gee) 12/6/85. One-liner by Aldous, 10/2/90.

294-039 and -063 965487 Summers, J.C., "Chinese hamster ovary cell assay for mutagenicity". Haskell Lab. Report No. 438-80, 5/16/80. The BH4 clone of the CHO-K1 cell line was used by method of A.W. Hsieh at Oak Ridge National Laboratory. 99.9 to 100% purity benomyl was tested in 4 trials with activation [from Aroclor 1254-induced CD rat livers] at concentrations up to 172 μ M and in 5 trials without activation at concentrations up to 805 μ M (typically two reps at each dose level in each trial). No treatment effect on chromosomal aberrations. **Unacceptable:** large variability between trials suggested technical problems; lack of QA/GLP. Original CDFA review by Wong, 5/10/85; one-liner by Aldous, 10/3/90.

294-140 123816 Reynolds, V. and Sarrif, A. "A Review of the Genetic Toxicity Studies on Benomyl and Carbendazim" (Haskell Laboratory, Du Pont, 1/93). In a review of genetic toxicity studies on benomyl and carbendazim, occasional positive findings were noted in many study types, including the Salmonella/Ames test (frameshift mutations), yeast and fungal reversion assays, mouse lymphoma assay, structural chromosomal aberration assay in human leukocytes, human/rodent hybrid cell assay (to quantitate chemically-induced aneuploidy), and the Sister Chromatid Exchange (SCE) assay in CHO cells. Although numerous genetic toxicity studies were cited which had positive responses, the authors concluded that impurities such as 2,3-diaminophenazine (DAP) that may arise during benomyl or carbendazim synthesis were responsible for the positive responses. The use of test compound with no more than 5 ppm DAP resulted in negative findings in the Ames test. Conflicting gene toxicity findings were also attributed to inadequate protocols or test systems, lack of supportive data, and the sensitivity of the test system (particularly in vitro mammalian systems) to cytotoxicity. According to the author, the only genotoxic endpoint showing a specific benomyl-related effect was numerical chromosome aberrations (aneuploidy).

Adverse effects from animal studies were also discussed, including acute dermal sensitization in guinea pigs, benign liver tumors in mouse chronic studies (possibly through induction of liver enzymes, modulating growth of spontaneous neoplasms), reproductive effects (eg. decreased sperm counts, decreased testicular weights and histopathologic changes) and developmental effects in rats and rabbits (anomalies of the eyes, skull and head). The liver was reported as the primary target organ as evidenced from serum enzyme changes, elevated organ weight and histopathic changes. No worksheet. Kellner, 9/24/93.

CHROMOSOMAL ABERRATION

BENOMYL

**** 294-117 088850** "Benomyl: Micronucleus Test in Mice." (Sasaki, Y. F. X., The Institute of Environmental Toxicology, Tokyo, IET 89-0046, 3/2/90) Benomyl, lot AG 0079-37, 95% pure, was given in a single dose by oral gavage at 0 (0.5% aqueous sodium carboxymethylcellulose), 1250, 2500 or 5000 mg/kg. Each group contained 6/sex with sacrifice times of 24, 48 and 72 hours. No mortalities were reported. No effect on the PCE/(PCE + NCE) was noted. Formation of micronuclei per 1000 polychromatic erythrocytes was evaluated. An increase in micronuclei formation in PCE's was reported at 24 and 48 hours with statistical significance at all three doses and at 72 hours, for 2500 and 5000 mg/kg. A statistically significant trend was also seen at 24 and 48 hours. **Possible adverse effect. Acceptable.** (Gee, 9/27/90)

294-117 088851 "In vivo Evaluation of IN T1991-259 for Chromosome Aberrations in Mouse Bone Marrow." (Stahl, R. G., Jr., Haskell Laboratory for Toxicology and Industrial Medicine, Report No. 401-90, 7/23/90) Benomyl technical, 96.1%, was given in a single dose by oral gavage to 5/sex/group of B6D2F1/Cr-1BR mice. Doses were 0 (corn oil), 625, 1250, 2500 or 5000 mg/kg. Cyclophosphamide was the positive control. Animals were sacrificed 24 hours after dosing and at least 2 slides/animal were prepared. When possible, 50 cells/animal were scored [by Hazleton Laboratory Americas] for chromosome and chromatid aberrations and the mitotic index recorded. **No increase in aberrations** at the 24-hour harvest time. **Unacceptable** (single sacrifice time without justification). (Gee, 9/28/90)

294-063 036286 (With rebuttal in -076, 043808): "Micronucleus Test on Benomyl," in mice; SRI, 2/12/80; benomyl, 1000, 500, 250, or 0 (DMSO) mg/kg once, kill at 48, 72, and 96 hours; 1000 mg/kg once with kill at 24 and 72 hours. Tested males only, 500 PCE's/animal. **Micronuclei** increased at 1000 mg/kg. Reviewer questioned solubility of AI at high dose, and whether mice received full dose. Rebuttal below cannot answer deficiencies, still **Unacceptable** and not **upgradeable**.

REVIEW: original 12/6/85, rebuttal 6/17/86, by (Remsen) Gee.

EPA One-liner: "Dose related significant increase in micronuclei in bone marrow from femur bones."

294-076 043808: Narrative rebuttal of #36286, does not address deficiencies: no females used, failure to sample at 12-24 hours in lower dose level groups, insufficient cells/animal scored, no positive control, and solubility problems with vehicle. One-liner added 9/8/87, Martz.

294-063 036282 (With rebuttal in -076, 43806): "Benlate - Dominant Lethal Study in Male Rats;" Haskell Laboratory, 3/28/74; benlate (54% AI) at 5000, 2500, 500 or 0 ppm (AI or bulk?) in the feed for 7 days; mated weekly for 6 weeks. No effects noted, but no positive control, too few animals, and other deficiencies [AI instability in feed] confounds interpretation. Contains no useful information. Rebuttal below does not upgrade status. **Unacceptable** and not **upgradeable**.

REVIEW: original 12/5/85, rebuttal 6/17/86, by (Remsen) Gee.

EPA One-liner: none in Branch Library.

294-076 043806: Narrative rebuttal to #36282 above attempting to justify dose level selection, dietary route of administration, and 7 day exposure period. Uncorrectable deficiencies cannot be addressed: mating performance of controls, lack of positive controls, and no feed analysis. One-liner added 9/8/87, Martz.

****294-112 075752** "Benomyl: In vitro Cytogenetics Test." (Institute of Environmental Toxicology, Tokyo, Japan, IET 88-0043, 11/28/88) Benomyl, Lot # F90707, 98.7%, tested with Chinese hamster lung (CHL) cells with and without male rat liver activation (Aroclor-induced); without activation, incubated for 24 or 48 hours, 2 cultures per concentration, two trials at 0 (non-treated and solvent - DMSO), 1.416,

2.832, 5.664, 11.33 or 22.66 µg/ml. With activation, treated for 6 hours, washed and incubated a further 12 or 18 hours, duplicate cultures, two trials. In trial 1, concentrations were 0, 3.119, 6.238, 12.48, 24.95 or 49.9 µg/ml. In trial 2, at 0, 5.664, 11.33, 22.66, 45.31, or 90.63. One hundred metaphases per culture were scored for polyploidy (37 or more chromosomes from a modal number of 25) and for chromatid/chromosome aberrations. Results were positive for **ADVERSE EFFECTS** on structural and numerical chromosomal aberrations with and without activation. Results without activation were greater than with activation. ACCEPTABLE study.

REVIEW: 9/21/89, by Gee.

EPA One-liner: None in Branch Library.

** **146 126870** "Classification of DPX-T1991-529 (Benomyl)-Induced Micronuclei in Mouse Bone Marrow Erythrocytes Using Immunofluorescent Antikinetochore Antibodies", (K.S. Bentley, E.I. DuPont De Nemours & Co., Haskell Laboratory for Toxicology and Industrial Medicine, HLR Report No. 568-92, 10/12/92). Benomyl technical [[1-[(butylamino)carbonyl]-1H-benzimidazol-2-yl]-carbamic acid, methyl ester], purity 96.1-97.4%, was administered in a single oral intubation at concentrations of 0 (0.5% methyl cellulose), 100, 2500, or 5000 mg/kg to 5 B6D2F1/Cr-1BR mice/sex/group. Test animals were sacrificed 48 hours after treatment. **Possible adverse effect: Increase in micronucleated polychromatic erythrocytes**; NOEL = 100 mg/kg. Micronuclei increases were primarily kinetochore positive, and, as a result, DPX-T1991-259 was classified as an aneugen. **Acceptable**. (Kishiyama and Gee, 8/30/96).

MBC

294-078 044579 (With rebuttal in -095, TAB 10): "The Specific Arrest of HeLa Cells in Mitosis by Methyl 2-Benzimidazolecarbamate;" du Pont, no date given; MBC, purity not given; cells exposed to 10^{-7} to 10^{-4} M or 20 µg/ml for various time periods; **ADVERSE EFFECT**: cell cycle progression was halted in mitosis, cells entered mitosis but could not divide to G1 stage; status not applicable for data requirement due to nonstandard design but otherwise well done and useful for genotoxic evaluation [referenced to be a spindle poison in mammalian toxicology reports and summaries].

REVIEW: 6/18/86 by (Remsen) Gee and 9/9/87 by Martz.

EPA One-liner: none in Branch Library.

294-095 TAB 10: Narrative rebuttal arguing for acceptability of #44579 based on study's scientific value and merit. The latter are agreed with, but study design is not applicable for specific data requirements in spite of good scientific merit. 9/9/87, Martz (no separate Worksheet).

*** COMMENT:-063, 036285 (With rebuttal in -076, 43807) was originally classified as 844 but can also fulfill 843 requirement. This report, whose one-liner is located below in "DNA CHANGES (BENOMYL)", in combination with # 044579 and # 036286 provide sufficient information to fill the chromosomal aberration data requirement. Added 9/9/87, Martz.

CONCLUSION: A "possible adverse effect" status is being assigned to this test category on the basis of 3/4 positive studies, one of which was acceptable. 9/16/87, Martz. Note: Additional positive studies have been reviewed. Gee, 9/3/96.

146 126869 "Classification of DPX-E965-299 (Carbendazim, MBC)-Induced Micronuclei in Mouse Bone Marrow Erythrocytes Using Immunofluorescent Antikinetochore Antibodies", (K.S. Bentley, E.I. DuPont De Nemours & Co., Haskell Laboratory for Toxicology and Industrial Medicine, HLR Report No. 569-92, 9/3/92). Carbendazim technical (1H-benzimidazol-2-yl-carbamic acid, methyl ester), purity 99.3%, was administered in a single oral intubation at concentrations of 0 (0.5% methyl cellulose), 66, 1646, or 3293 mg/kg to 5 B6D2F1/Cr-1BR mice/sex/group. Test animals were sacrificed 48 hours after treatment.

Possible adverse effect: Increase in micronucleated polychromatic erythrocytes; NOEL = 66 mg/kg. Micronuclei increases were primarily kinetochore positive. As a result, DPX-E965-299 was classified as an aneugen. **Supplemental data.** (Kishiyama and Gee, 8/29/96)

CHROMOSOMAL EFFECTS: ADDITIONAL INFORMATION (ESPECIALLY PUBLICATIONS)

294-064 036303 Bignami, M., Aulicino, F., Velcich, A., Carere, A., and Morpurgo, G. "Mutagenic and recombinogenic action of pesticides in *Aspergillus nidulans*". *Mutation Res.* 46:395-402 (1977). Benomyl (2 mg per 3 cm x 5 cm filter paper triangle) induced a high frequency of mitotic non-disjunction in *Aspergillus nidulans* in the spot test. Benomyl at 0.4 µg/ml also promoted non-disjunction in *Aspergillus* in a "non-selective" test. **Unacceptable** due to limitations in study design. **Possible adverse effect indicated.** de Vlaming/Apostolou, 12/3/85.

294-064 036306 Seiler, J.P. "The mutagenicity of benzimidazole and benzimidazole derivatives. VI. Cytogenetic effects of benzimidazole derivatives in the bone marrow of the mouse and the Chinese hamster." *Mutation Res.* 40:339-348 (1976). MBC at doses of 100 mg/kg or above was mutagenic in mice in the micronucleus test. Benomyl at 1000 mg/kg was positive in the same test. Doses were given twice and the mice sacrificed 6 hours after the second dosing. **Unacceptable** due to limitations in study design. **Possible adverse effect indicated.** de Vlaming/Apostolou, 12/4/85; updated by Gee, 10/1/90.

294-064 036307 Richmond, D.V., and Phillips, A. "The effect of Benomyl and Carbendazim [MBC] on mitosis in hyphae of *Botrytis cinerea* Pers. ex Fr. and roots of *Allium cepa* L." *Pesticide Biochem. Physiol.* 5:367-379 (1975). Benomyl and MBC at 100 µg/ml induced chromosome aberrations in hyphae of *Botrytis cinerea* and root tips of onion *Allium cepa*. **Unacceptable** due to limitations in study design. **Possible adverse effect indicated.** de Vlaming/Apostolou, 12/4/85.

294-063 036288, 036289 Lamb, M.J., and Lilly, L.J. "An investigation of some genetic toxicological effects on the fungicide Benomyl". *Toxicology* 17:83-95 (1980). [see also CDFA review of the recessive lethal portion of this report, under Record No. 036287]. To evaluate chromosome loss or breakage in *Drosophila*, either 1 mg/ml Benlate* (powdered formulation which is 50% Benomyl) or 0.5 mg/ml MBC was dissolved in 0.5% DMSO. Benomyl and MBC were fine suspensions at these concentrations. Food and water were withheld from adult male *D. melanogaster* [$yw^+B/B^S Y^+$ strain] flies for 16 hr, then flies were placed in the presence of a drop of Benomyl, MBC, or DMSO vehicle. Differences in weights of groups of 5 flies were taken as estimates of consumption. Neither Benomyl nor MBC increased the numbers of offspring resulting from paternal chromosome losses, exchanges, or breaks. The human lymphocyte study involved blood samples cultured with MBC for 44 hr. Chromosomes from cells cultured with MBC were more contracted than controls, however MBC did not increase the numbers of cells with chromosome aberrations. Thus both studies were negative. Original brief CDFA reviews by Remsen (Gee) 12/6/85. One-liner by Aldous, 10/2/90.

294-063 036291 (also 036290 and 036292) Ruzicska, P., Pe'ter, S., Laczi, J., and Czeizel, E. "Study on the chromosome mutagenicity of Fundazol 50WP". *Ege'sze'gtudoma'ny* (Budapest) 20:74-83 (1976). Fundazol 50WP is similar to Benlate* formulation. Rats ("of R Amsterdam and Long Evans type") were used to derive (1) bone marrow cell suspension samples of 21-day pregnant rats for chromosomal aberration analyses, and to derive (2) embryonic tissues (of unspecified gestational age) for culturing in Parker 199 solution with 20% calf serum, for chromosomal aberration analyses, as above. At least the first of these rat studies involved gavage of dams on days 7 through 14 with 25, 50, 200, or 500 mg/kg/day Fundazol WP. In addition, peripheral blood samples of 20 male workers in a Fundazol WP plant were compared with those of 15 controls for chromosomal aberration analyses, as above. The bone marrow samples, and the worker epidemiological studies were negative. The investigators

concluded that "in the rat-embryonic tissue the ratio of chromosome aberrations considerably increased" (chromosome aberration incidence was reported to be statistically significant in 200 and 500 mg/kg/day groups). This is technically a "**possible adverse effect**", however the report is not sufficiently complete nor are the methods sufficiently validated to be useful for quantitative risk analysis. **Unacceptable**. Review by Remsen (Gee), 12/6/85; one liner updated by Aldous, 10/3/90.

DNA DAMAGE/REPAIR

BENOMYL

****294-063 036285** (With rebuttal in -076, 43807): "An Evaluation of the Effect of Benomyl on Sister Chromatid Exchange Frequencies in Cultured Chinese Hamster Ovary Cells;" SRI, 8/80, benomyl, 99% pure; CHO cells with S9 (F344) activation at 150, 75, 37.5, 18.8, 9.4, or 0 µg/ml for 2 hours; or without activation at 10, 5, 2.5, 1.25, 0.63, or 0 µg/ml for 22 hours. SCE increase at all concentrations tested both with and without activation, but high background rate confounds interpretation. Originally unacceptable but upgraded to **ACCEPTABLE** by rebuttal, with **ADVERSE EFFECT** noted.

REVIEW: original 12/5/85, rebuttal 6/17/86, both by (Remsen) Gee.

EPA One-liner: "Weakly positive for sister chromatid exchange."

COMMENT: This report can satisfy an 843 requirement also.

294-076 043807: Narrative rebuttal to # 036285 addressing inconsistency between cytogeneticists, cell cycle delay evaluation and test article stability. To quote: "...these deficiencies are irrelevant since the test material was shown to induce SCE's in CHO cells with and without metabolic activation." The rebuttal upgraded study to acceptable. One-liner added 9/9/87, Martz.

MBC

****294-078 044575** (With rebuttal in -095, TAB 7): "The Hepatocyte Primary Culture/DNA Repair Assay on Compound 11,201-01 Using Mouse Hepatocytes in Culture;" Naylor Dana Institute, 10/20/81; MBC, purity not given; B6C3F₁ male hepatocytes with 18-20 hour exposure to 0, 0.0125, 0.125, 1.25, 12.5, or 125 µg/ml; no effect reported; originally unacceptable but upgraded to **acceptable** with rebuttal in -095, TAB 7 (see below).

REVIEW: Original 6/18/86 by (Remsen) Gee, rebuttal response 9/9/87 by Martz.

EPA One-liner: "Not a mutagen when tested for DNA repair using mouse and rat hepatocyte cultures."

294-095 TAB 7: Narrative rebuttal to # 044575 adequately answering concerns of hepatocyte viability, number of cells scored, and test article purity. Upgraded study to acceptable. 9/9/87, Martz.

****294-078 044576** (With rebuttal in -095, TAB 8): "The Hepatocyte Primary Culture/DNA Repair Assay on Compound 11,201-01 Using Rat Hepatocytes in Culture;" Naylor Dana Institute, 10/20/81; MBC, purity not given; male F344 rat hepatocytes with MBC at 0, 0.0125, 0.125, 1.25, or 12.5 µg/ml; 125 µg/ml was toxic; triplicate cover slips, 2 trials, autoradiography; no evidence of unscheduled DNA synthesis; originally unacceptable but upgraded to **acceptable** with rebuttal in -095, TAB 8 (see below).

REVIEW: Original 6/18/86 by (Remsen) Gee, rebuttal response 9/9/87 by Martz.

EPA One-liner: "Not a mutagen when tested for DNA repair using mouse and rat hepatocyte cultures."

294-095 TAB 8: Narrative rebuttal to # 044576 adequately answering concerns of hepatocyte viability, number of cells scored, and test article purity. Upgraded study to acceptable. 9/9/87, Martz.

294-078 044571: "Mutagenicity Testing on Fungicide 1991 Metabolite (MBC) in Microbial Systems,"

Bacillus subtilis; Institute of Environmental Toxicology (Japan), 10/17/77; MBC, 99% pure; M45 and H17 without activation with 0, 20, 100, 200, 500, or 1000 µg/10 mm disk in 20 µl; no evidence of differential growth inhibition or cytotoxicity; **unacceptable** and not **upgradeable** (no activation).

REVIEW: 6/16/86 by (Remsen) Gee.

EPA One-liner: none in Branch Library.

CONCLUSION: A "possible adverse effect" status is being assigned to this test category on the basis of 1/3 acceptable studies being positive. 9/16/87, Martz.

DNA DAMAGE/REPAIR: ADDITIONAL INFORMATION (ESPECIALLY PUBLICATIONS)

294-064 036309 Kappas, A., Georgopoulos, S.G., and Hastie, A.C. "On the genetic activity of benzimidazole and thiophanate fungicides on diploid Aspergillus nidulans". Mutation Res. 26:17-27 (1974). Benomyl induced genetic segregation (haploidization) in a diploid strain of Aspergillus nidulans. **Unacceptable** due to limitations in study design. **Possible adverse effect indicated.** de Vlaming/Apostolou, 12/4/85.

294-064 036311 Morpurgo, G., Bellincampi, D., Gualandi, G., Galdinelli, L., and Serlupi Crescenzi, O. "Analysis of mitotic nondisjunction with Aspergillus nidulans". Environ. Health Perspect. 31:81-95 (1979). A plate test and a liquid test were performed with Benomyl and MBC. Both were positive for nondisjunction, apparently due to interference with spindle fiber formation. **Unacceptable** due to limitations in study design. **Possible adverse effect indicated.** de Vlaming/Apostolou, 12/4/85.

294-064 036312 Tates, A.D. "Microtus oeconomus (Rodentia), a useful mammal for studying the induction of sex-chromosome nondisjunction and diploid gametes in male germ cells." Environ. Health Perspect. 31:151-159 (1979). Contents of seminiferous tubules of field voles were examined at 1-16 days following MBC (2 gavage treatments, 24 hr apart, of 250 mg/kg MBC in gum arabic) or 1-14 days following Benomyl treatment (single ip injection of 50, 250, or 500 mg/kg Benomyl, with sacrifice for examinations of seminiferous tubules at varying times, generally 10 to 14 days). Frequencies of non-disjunction spermatids or of diploid spermatids were measured. Data for Benomyl were reportedly negative, but investigators concluded that "MBC was effective in inducing nondisjunction in young primary spermatocytes (day 10 after treatment)". The investigator noted that these results were "preliminary". **Unacceptable** due to limitations in study design. **Possible adverse effect indicated.** de Vlaming/Apostolou, 12/4/85: one-liner updated by Aldous, 9/28/90.

294-041 and -063 965490 Shirasu, Y., Moriya, M., and Kato, K., "Mutagenicity testing on Fungicide 1991 in microbial systems". Institute of Environmental Toxicology, Tokyo, 1/23/78. A (negative) rec assay as part of a series of studies on Benomyl. These studies were classified as **unacceptable**. One-liner for this report is near the end of the "Gene Mutation" section of this Summary. Aldous, 10/2/90.

294-041 038196 (the rec-assay portion of a series of studies). Shirasu, Y., Moriya, M., and Kato, K.; "Mutagenicity testing on Fungicide 1991 metabolite (MBC) in microbial systems". Institute of Environmental Toxicology, Tokyo, 10/17/77. MBC, 99%, was tested in the same systems as reported for Benomyl, above (294-041 and -063 965490). All results were negative. These studies were classified as **unacceptable**. One-liner for this report is near the end of the "Gene Mutation" section of this Summary. Aldous, 10/2/90.

294-039 965492 Tong, C., "The hepatocyte primary culture/DNA repair assay on Compound 10,962-02 [Benomyl] using rat hepatocytes in culture." Study apparently was performed at Naylor Dana Institute, Valhalla, NY; report issued 10/20/81. Seeded hepatocytes were treated with tritiated thymidine in the

presence of 0.00005, 0.0005, 0.005, 0.05, or 0.5 mg/ml Benomyl. Nuclear grain counts above background [minimum of 5 counts/nucleus to be "positive"] were recorded. Results were negative, by those criteria. Report is classified as **unacceptable**: inadequate description of test article, no analysis of dosing solution, insufficient individual data, no justification for the wide range of dosages selected, no QA/GLP. Original review by Wong, 5/9/85. One-liner by Aldous, 10/3/90.

294-039 965493, 965494, and 965495 Studies identical to 965492, above, except that -492 and -493 tested Benomyl, whereas the latter two tested MBC; and the even-numbered reports used F344 rat hepatocytes, whereas the odd-numbered reports used B6C3F1 mouse hepatocytes. All tests were negative, and all are classified **unacceptable** for the reasons given in the 1-liner above. Original reviews by Wong, 5/9/85. One-liner by Aldous, 10/4/90.

Note that one of these reports, 965494, was submitted separately and given document:record number 294-078:044576. The latter study was eventually upgraded to acceptable status following submission of additional information (see 1-liner, about 3 pages toward the front of this Summary).

294-039 965488 A summary of journal articles and studies concerning the oncogenic, mutagenic and reproductive toxicity potential of Benomyl. Duplicate of record -063:36297. No worksheet. Kellner, 9/24/93.

NEUROTOXICITY STUDIES

BENOMYL

161 131147 Foss, J. "Subchronic Neurotoxicity Study of DPX-T1991-529 (Benomyl) Administered Orally Via The Diet To CrI:CD*BR VAF/Plus® Rats" (Argus Research Laboratories, Inc., Report No. 104-019, DuPont Study #HLO 551-93, 6/13/94). Benomyl (Lot No. F60317K, 97.4% purity) was administered orally via the feed to 11 CrI:CD® BR VAF/Plus® (Sprague-Dawley) rats/sex/dose at levels of 0, 100, 2500 or 7500 ppm for 92 to 95 consecutive days. Feed consumption and body weight gain was reduced in high-dose rats. Motor activity (total movements) for high-dose males was increased 40%, 56% and 48% in weeks 4, 8 and 13, respectively; similar increases were seen in high-dose females. No compound-related FOB findings, gross or microscopic neuronal lesions were reported. NOEL (for body weight and motor activity effects) = 2500 ppm. **No Adverse Neurotoxic Effects. ACCEPTABLE. Kellner, 1/25/95.

-143 125046 Foss, J. "Acute Neurotoxicity Study of DPX-T1991-529 (Benomyl) Administered Orally Via Gavage to CrI:CD® BR VAF/Plus® Rats" (Argus Research Laboratories, Inc., Report No. HLO 825-92, 6/14/93). Benomyl (Lot No. F60317K, 97.4% purity) was administered orally via gavage to 10 CrI:CD® BR VAF/Plus® (Sprague-Dawley) rats/sex/dose at levels of 0, 500, 1000 and 2000 mg/kg. By day 2, most of the high-dose males and one female showed soft or liquid feces during the Functional Observation Battery (FOB). Between day 1 and 3, 1 female each in the mid- and high-dose groups showed urine-stained fur during clinical observations and FOB. Number of movements and time spent in movement was reduced in high-dose females on the day of dosage. Body weight gain was reduced in all dose groups on day 1 and 2 (statistically significant in the mid- and high-dose males only) accompanied by significantly reduced feed consumption values (all males and mid-, high-dose females). Systemic NOEL < 500 mg/kg. **No Adverse Neurotoxic Effects.** Acceptable as supplementary data. Kellner and Aldous, 11/10/93.

-141 124974 Interim report (2 pages) for acute neurotoxicity study -143: 125046. No Worksheet. Kellner, 2/15/95.

294-065 036332 (With rebuttal in -076, 043801 & -02): "Neurotoxicity Study in Hens;" IRDC, 6/5/78; benomyl (H-10962, purity not given), 5000, 2500, 500, or 0 mg/kg by oral gavage with TOCP at 750 mg/kg as positive control; results equivocal because study compromised due to intercurrent disease, has no useful data. Not acceptable, but not a required test.

REVIEW: original 11/25/85 by Apostolou, rebuttal 6/11/85 by Martz.

EPA One-liner: "Inconclusive results due to underlying disease in hens." No grade given.

294-076 043801 & -02: Rebuttal to # 036332 above. Clarifies nerve selection 29 for histopathology and absence for forced activity assessment as well as a revised pathology report consisting of the opinions of 5 pathologists about the equivocal findings. One-liner added 9/8/87, Martz.

BENOMYL

294-065 036331 (With rebuttal in -076, 043803): "Acute Delayed Neurotoxicity Study in Chickens;" IRDC, 12/7/79; benomyl (H-10962, purity not given), 5000, 2500, 500, or 0 mg/kg by oral gavage with TOCP at 1200 mg/kg as positive control; death, ataxia, low carriage, and wing drop at 5000 mg/kg, but 2500 and 500 mg/kg groups asymptomatic; no histological evidence of delayed neurotoxicity. Rebuttal (below) clarified major criticisms. INCOMPLETE but upgradeable, however not a required test.

REVIEW: original 11/25/85 by Apostolou, rebuttal 6/11/86 by Martz.

EPA One-liner: "No evidence of delayed neurotoxicity was found." No grade given.

294-076 043803: Narrative rebuttal to # 036331 above. Clarifies nerve selection for histopathology, not having used atropine protection, no repeat dosing on day 21, and the consistency of results with the previous equivocal study (#36332). One-liner added 9/8/87, Martz.

MBC

294-077 044556 & -7: "Neurotoxicity Study in Hens;" IRDC, 6/5/78; MBC (H-11,201, purity not given), 5000, 2500, 500, or 0 mg/kg by oral gavage with TOCP at 750 mg/kg as positive control; clinical signs of neurotoxicity at 5000 mg/kg; no histopathologic evidence of neurotoxicity in any MBC treated hens; INCOMPLETE BUT UPGRADEABLE with additional information, however, not a required test.

REVIEW: 6/13/86 by Martz. (No EPA 1-liner on file with CDFA).

APPENDIX B

OCCUPATIONAL EXPOSURE ASSESSMENT

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN BENOMYL

by

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HS-1557

August 5, 1998

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ABSTRACT

Benomyl, (methyl 1-(butylcarbamoyl)-2-benzimidazole carbamate) is a broad spectrum fungicide registered for use on a wide variety of agricultural crops and for home owner use on lawns, ornamentals and home garden vegetables. The risk characterization document for benomyl, prepared by the Medical Toxicology Branch of the Department of Pesticide Regulation, indicates that a metabolite of benomyl, methyl 2-benzimidazole carbamate (MBC), has the potential to cause developmental toxicity in rabbits. The United States Environmental Protection Agency has classified benomyl as a group C oncogen (possible human carcinogen) in the Guidance Document for the Reregistration of Pesticide Products that Contain Benomyl as the Active Ingredient (June 1987). Dermal absorption of benomyl is estimated to be approximately 10% over a 24-hour period. Benomyl degrades primarily by removal of the butylcarbamoyl group, leaving MBC and butyl isocyanate. Animal feeding studies have identified the primary metabolites of benomyl as MBC, its hydroxylated metabolite 5-OH MBC and 2-aminobenzimidazole and its 5-hydroxylated metabolite. Excretion of metabolized benomyl in the urine and feces of mice was found to be 95% complete 96 hours after oral administration. Exposure data from the Pesticide Handlers Exposure Database was used to quantify the occupational exposure to benomyl from applying Benlate[®] SP Fungicide. The estimated dermal exposure for flaggers, mixer/loaders and applicators ranged from 1.0-7.8 mg per workday (8 hours) with inhalation exposures ranging from 0.003-1.5 mg. Field workers pulling leaves or thinning shoots in a vineyard treated with Benlate[®] SP Fungicide at the maximum label rate could experience a dermal exposure of 25.9-31.7 mg of benomyl per day.

APPENDIX B

California Environmental Protection Agency Department of Pesticide Regulation, Worker Health and Safety Branch

Human Exposure Assessment for Benomyl August 5, 1998

GENERAL PHYSICAL AND CHEMICAL CHARACTERISTICS

Benomyl (methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate) is a broad spectrum fungicide of low acute mammalian toxicity. The pure compound has a molecular weight of 290.3 and consists of colorless crystals with a vapor pressure of 3.7×10^{-8} mm Hg at 25° C (Barefoot, 1988). It decomposes at high temperatures or in the presence of either acid or alkali conditions. It is soluble in water to the extent of approximately 2 ppm and will form a 9.4% solution in chloroform, 1.8% in acetone and 0.4% in ethanol.

EPA STATUS

The United States Environmental Protection Agency (U S EPA) has conducted several extensive reviews of the data supporting the registration of benomyl and has classified this compound as a Group C Oncogen (U S EPA, 1987). In regard to occupational exposure, the position document (PD 4) issued on October 29, 1982 (U S EPA, 1982) required either cloth or disposable dust masks to be worn by mixer/loaders of aerial application equipment. The guidance document for the reregistration of benomyl products was issued in June 1987. Manufacturers were required to submit foliar and soil dissipation studies and additional dermal and inhalation studies. An interim worker reentry interval of 24 hours was established (prior to August 1992) on all crops treated with benomyl until the data can be generated. The Agency has also mandated amendments to the benomyl label to provide protective clothing for mixer/loaders and applicators. The required clothing is listed in the "Personal Protective Equipment" section of this assessment. To date, the primary registrant has continued to support benomyl in the reregistration process. The U S EPA is reviewing submitted data and waiting for additional data to be generated from the required studies that are in progress.

USAGE

The benomyl product registered for agricultural uses has recently undergone a significant loss in uses for California crops. Uses on all ornamental crops, and on avocados and rice have been dropped from the Benlate® SP Fungicide label. Benomyl is still registered for use as a seed treatment, a bulb dip, and as a broadcast spray on conifers and many vegetable, field and orchard crops. The dip treatments require 8 oz. active ingredient (a.i.)/100 gallons of water. Seed treatment uses range from 4 to 16 oz. a.i. per 100 lbs. of seed. Sprays for crops are applied in the

range of 2-16 oz. of a.i./acre. The application rates for the home/garden labels are 1-2 oz. of a.i. per 1,000 square feet of lawn and 0.5-1 oz. a.i. per 12.5 gallons of water on garden fruits and vegetables. Over 150,000 lbs. of benomyl were reported used in 1994 by the California Environmental Protection Agency (Cal/EPA), Department of Pesticide Regulation (DPR, 1996). The majority was used on almonds, celery, grapes, stone fruits and strawberries.

FORMULATION

Two products formulated as a 50% wettable powder of benomyl, are currently registered in California. Benlate® SP by Du Pont Chemical is registered for agricultural uses and is packaged in one-pound water soluble packets. A second product, Green Light Systemic Fungicide with Benomyl, is registered for home-garden uses. The product manager at the Green Light Company has indicated that the product is currently registered only to cover the product that may still be in the channels of trade (Luedke, 1997). Du Pont Chemical is no longer selling technical benomyl for use in formulating home-garden products. The Green Light Company has ceased manufacturing this product and does not have any in storage. It seems appropriate to conclude that the home-garden use of benomyl will not exist in a year or two.

LABEL PRECAUTIONS

The label signal word on all formulations is "Caution". This is primarily due to the fact that benomyl is a mild irritant to the eyes, nose, throat and skin. Labels advise the user to avoid contact with skin, eyes and clothing and to avoid breathing dusts and spray mists. In the event of contact with the concentrate or spray mixture, flush skin and eyes with plenty of water; for eyes get medical attention. The possibility of exposure causing a temporary allergic skin reaction for sensitive individuals is mentioned on the label registered for agricultural uses.

PERSONAL PROTECTIVE EQUIPMENT

Workers with the potential for exposure to benomyl during application of Benlate® SP Fungicide or other work tasks must wear long pants and long-sleeved shirt or coveralls, full body chemical-resistant clothing, waterproof gloves and chemical-resistant footwear plus socks and a dust/mist filtering respirator. In addition, workers mixing and loading concentrate benomyl must also wear a chemical-resistant apron. A closed system is required for the transfer of the liquid mixture from the mix tank to the application tank. If the application is going to be made in an enclosed area like a mushroom propagation house, an organic vapor respirator for pesticides must be worn instead of a dust/mist filtering respirator. Farm workers entering treated areas prior to the expiration of the 24-hour reentry interval, must wear work clothing, waterproof gloves, chemical-resistant footwear plus socks. If an aerial applicator is using aircraft with an enclosed cockpit, only a long sleeved-shirt and long-legged pants, shoes and socks need be worn. However, a pair of chemical-resistant gloves must be available in the cockpit and be worn when entering or

leaving an aircraft contaminated with pesticide residues. Flaggers must be in totally enclosed vehicles.

The use of a product formulated in water soluble packets in conjunction with the label requirement to use a closed system to transfer the liquid mixture complies with the definition of a "closed system" for California and federal regulations. The federal Worker Protection Standards (WPS) and the California regulations to implement WPS allow employees mixing and loading a category III pesticide with a closed system to substitute long-sleeved shirt and long pants or coveralls, and shoes and socks for the label-required PPE*. The WPS also permits flaggers working in an enclosed cab without air filtration, to wear only work clothing and the respirator required by the label for handlers. Although the product label does not address protective eye wear, the federal WPS and the California regulations to implement WPS, require eye protection to be worn by employees mixing and loading pesticides with a closed system operated under positive pressure*. Since aircraft with enclosed cabs are the standard of the aerial application industry, the aerial applicator was assumed to be operating an airplane with an enclosed cab. However, for ground boom and orchard-vineyard air-blast applications the operator was assumed to be operating equipment with an open cab.

WORKER ILLNESSES

Reports of illness attributed to exposure to combinations of pesticides which include benomyl are more common than those attributed to benomyl alone. This reflects the practice of using multiple fungicides to avoid selecting resistant strains. The majority of reports concern skin rashes. Since benomyl is known to be a sensitizing agent, it is possible that some of the rashes reported represent allergic dermatitis (Gargus, 1984).

During the years 1984 - 1993, eight systemic illnesses attributed to benomyl exposure were reported by the Cal/EPA, Department of Pesticide Regulation (DPR) (CDFA, 1985; CDFA, 1986; CDFA, 1987; Edmiston and Richmond, 1988; Mehler *et al.*, 1990; Mehler, 1991; DPR, 1993; DPR, 1994a; DPR, 1994b; DPR, 1995). In addition, for the same period, seven skin and three eye injuries were attributed to benomyl alone, while nine skin, seven eye, one involving both eye and skin and five systemic illnesses were attributed to exposure to benomyl in combination with other pesticides.

DERMAL TOXICITY

Benomyl is known to provoke allergic responses in people, although the original tests on guinea pigs were negative for sensitization (Du Pont, 1986). Repeated tests indicated mild sensitization

* Current California regulations allow employees mixing and loading with a closed system to substitute work clothing, a chemical resistant apron, boots and gloves for full body chemical-resistant clothing. Protective eyewear must also be worn during mixing and loading with a closed system when making and breaking connections and during all hand and most ground applications.

of guinea pigs (Du Pont, 1986). Tests on rabbits and guinea pigs showed mild to moderate irritation at concentrations above 40% (Du Pont, 1986). No dermal LD₅₀ could be determined; the highest practical dose of 10 g/kg, (occluded for 24 hours) resulted in some weight loss without other apparent toxicity (Du Pont, 1986).

DERMAL ABSORPTION

Dermal absorption was investigated using albino rats (Belasco *et al.*, 1981). Benlate® (trade name of benomyl in wettable powder) labeled with ¹⁴C was applied in water suspension to four square inches on the backs of rats at rates of 0.2, 2, 20 and 200 mg of product per rat. This corresponds to concentrations of 4, 40, 400 and 4000 µg a.i./cm². Groups of four rats each at each dose level were sacrificed at 0.5, 1, 2, 4 and 10 hours following dosing. The maximum blood level was reached within four hours with only a slight increase from the level observed after one hour. Urinary excretion was appreciable even during the first half hour.

Analysis at the U S EPA included an estimate of the maximum obtainable blood levels from a semilogarithmic plot of rat blood level versus dose rate. The rat data was plotted as a log-log plot of excretion versus dose rate and used to estimate a human absorbed dose (U S EPA, 1979). The conclusions were that the maximum potential blood concentration is less than 130 ppm, which was stated to be a non-toxic dose. A study by Jegier (1964) cited in the benomyl position document, concluded that a mixer/loader exposed dermally to 1.8 mg/kg/hour of benomyl would absorb 374 micrograms during the course of an eight-hour workday.

The assumptions involved in the U S EPA estimate of absorption by a mixer/loader differ from those that are standard at DPR. Computations by the U S EPA were limited to unprotected skin areas (260 square inches). Only the absorption that would occur during the workday was considered, and the amount of chemical on the skin was considered to accumulate hour by hour.

DPR policy is to consider exposure to the entire body, not just unprotected areas, and to compute absorption potential for a whole day's accumulation left in contact with the skin for 10-24 hours. This can be estimated from urinary excretion data provided in the dermal absorption study. The rate of urinary excretion was quite consistent at each dose level. Extrapolation of urinary recovery at 2, 4 and 10 hours to 24 hours results in apparent absorption of 10% of the 4 µg/cm² dose, 1.5% of the 40 µg/cm² dose, 0.3% of the 400 µg/cm² dose, and 0.1% of the 4000 µg/cm² dose. Since the dermal exposure from occupational activities is expected to average less than 5 µg/cm², the 10% absorption rate was used in the exposure assessment to calculate the absorbed dose from a dermal exposure.

ANIMAL METABOLISM AND DEPOSITION

Benomyl degrades primarily by removal of the butylcarbamoyl group, leaving methyl 2-benzimidazole carbamate (MBC, or carbendazim) and butyl isocyanate (Kilgore and White, 1970). Butyl isocyanate degrades rapidly and irreversibly to carbon dioxide and butylamine

(Krupka, 1974). In water, the estimated half-life is 14 minutes (Moye *et al.*, 1994). MBC is a fungicide of equivalent effectiveness and range to benomyl. MBC is considered by some to be the active form of the pesticide, especially since MBC is also the degradation product of another broad spectrum fungicide, thiophanate-methyl (U S EPA, 1982). The impression that conversion of benomyl to MBC was rapid and quantitative may be due to a laboratory artifact (Baude *et al.*, 1973). A recent DFR study conducted by one of the registrants indicated the half-life in the field is much longer. DFR on grapes treated late in the season with 0.75 lb a.i./acre had a half-life of approximately 21 days (Powley, 1989). A similar study conducted on strawberries observed a half-life of about seven days (Mc Nally, 1990).

The fate of ingested benomyl was investigated in rats, dogs, cows and hens by Gardiner *et al.* (1974) and in mice, rabbits and sheep by Douch (1973). The registrant has submitted studies on oral, intravenous and dermal administration of benomyl to rats and mice (Belasco *et al.*, 1981), (Haskell Laboratory, 1980a and 1980b). Excretion of benomyl in urine and feces of mice was found to be 95% complete 96 hours after oral administration (Douch, 1973). Following intravenous administration, elimination was over 95% complete in 24 hours (Belasco *et al.*, 1981). Dosing of pregnant rats by gavage resulted in very early peaks of benomyl/MBC concentrations both in maternal blood and embryonic tissue (Haskell Laboratory, 1980a). The hydroxylated metabolite, 5-OH MBC, was eliminated more slowly, with a half-life of 2-3 hours in maternal blood and 4-8 hours in embryonic tissue. Douch also identified 2-aminobenzimidazole (2-AB) and its 5-hydroxylated metabolite as significant metabolic products of benomyl.

Although data have not been submitted on human metabolism, the studies of various animal species indicate reasonably rapid and quantitative elimination in urine of a sufficiently small set of metabolites that biological monitoring may be practical. The relevant animal data are summarized in Table 1.

Table I Quantitation of Benomyl Metabolites in the Excreta of Various Test Species

Subject Recovered Species	Reference	Source Administration	Route of Period	Collection Analyzed	Matrix			Percent of Dose	
					Benomyl	MBC	5-HBC	2-AB	5-OH-2-AB
rat	Gardiner <i>et al.</i> , 1974	oral	72 hrs	urine	<5 ^a	<5 ^a	~75		
dog	Gardiner <i>et al.</i> , 1974	oral	72 hrs	feces	-	~70	~10		
mouse	Douch, 1973	oral/IP	96 hrs	urine	ND ^b	30	8	12	5
				feces	ND	15	9	8	5
rabbit	Douch, 1973	oral	96 hrs	urine	ND	23	11	11	10
				feces	ND	4	8	12	4
sheep	Douch, 1973	oral	96 hrs	urine	ND	19	11	24	3
				feces	ND	4	8	12	4
rat	Belasco <i>et al.</i> , 1981	dermal	10 hrs	urine	-	"lesser"	"major"		
rat	Belasco <i>et al.</i> , 1981	IV	6 hrs	urine	-		84-108		

Melher, WH&S, 1991

^a The dose recovered from each of the samples was less than 5%.

^b ND = none detected; '-' symbol is used when data are not presented.

OCCUPATIONAL EXPOSURE

A review of the available toxicological data by the Medical Toxicology Branch has indicated that an occupational risk for tumors may exist for workers experiencing chronic exposure to benomyl. An estimate of the chronic exposure for workers handling Benlate® can be derived from studies that observe the exposure from one day's work. From this single day exposure an absorbed daily dosage (ADD) can be estimated with the dermal absorption rate and a standardized body weight. If the number of days per year a worker handles a specific pesticide can be estimated, then the average annual daily dosage (AADD) and a lifetime average daily dosage (LADD) can be calculated. Since field workers have potentially longer work seasons that involve exposure to benomyl, the oncogenic risk from working in Benlate® treated crops should be derived from the average daily exposure for the work season for the purpose of deriving the AADD and LADD.

I. APPLICATION:

The data available for evaluating the occupational exposure to benomyl is very limited. A data search of the Pesticide Registration Library on December 27, 1996 yielded only one study that monitored the exposure to benomyl from applying Benlate® to currently registered crops. The study by Everhart and Holt (1982) observed the exposure to benomyl for workers mixing and loading Benlate® for aerial applicators. Surgical gauze pads were used to observe the dermal exposure to the forearms, face, back and chest. Cotton gloves were used to detect exposure to the hands. The other body regions, thighs, legs and portions of the back and chest were considered protected by work clothing and exposure was not monitored. Ten replicates of the mixing/loading work task, lasting 1.5-5 minutes each, were observed. The composite dermal exposure estimated from the pads worn by each worker was calculated using a body surface area of 2,940 cm². The standardized body surface area for a 75.9 kg male worker is 19,400 cm² (Thongsinthusak *et al.*, 1993). Pesticides, even in the wettable powder formulation, have the ability to penetrate work clothing. The standard protection value used by the Worker Health and Safety Branch for work clothing is 90% with 10% penetration (Thongsinthusak *et al.*, 1993). The study is deficient in that the replicates were too short in duration and the patch monitoring did not represent several large body areas.

Exposure information is available in the Position Document 4 for Benomyl/Thiophanate-Methyl (U.S EPA, 1982). However, most of this information is derived from exposure data of other chemicals. The summaries are very brief with no details of the studies themselves other than the observed values. Without any background information on the surrogate studies used to derive the exposure estimates, it is not possible to evaluate the quality of the surrogate data.

The available data for benomyl is too limited in scope to be useful for estimating the occupational exposure from applying Benlate®. The Pesticide Handlers Exposure Database (PHED, 1995) was used to derive estimates of the exposure to benomyl for the various application methods. As a database composed of the results from studies which did not follow a standardized protocol, PHED has limitations to its use as a surrogate database.

The PHED database was constructed as a summary of the exposure data from many studies, each with a different minimum detection level (MDL) for the analytical method used to detect residues

in the sampling media. And since the detection of dermal exposure to the body regions was not standardized, some studies observed exposure to only selected body regions such as the hands, arms and face, with the other body regions considered 100% protected from exposure by work clothing. As a consequence the subsets derived from the database for dermal exposure have different number of observations (n) for each of the body regions.

The calculation of a standard deviation for the mean dermal exposure rate for the whole body is therefore not appropriate because the mean rate was derived as the sum of the mean rates for each body region which were derived from various numbers of observations (replicates). Although confidence intervals were provided for the derived mean dermal and inhalation rates, they may not represent an accurate expression of their variability. The physical properties of each pesticide were not included in the selection criteria for the database. As a consequence, the surrogate data derived for a specific pesticide can not be subsetted on the basis of similar physical properties such as vapor pressure, etc. Despite these limitations, PHED was used to derive data subsets that estimate the occupational exposure to benomyl for work tasks related to the application of Benlate® SP Fungicide.

The occupational exposure incurred for workers mixing and loading benomyl formulated in water soluble packets was estimated from a subset generated with the following selection criteria. The criteria for the minimum number of lbs. a.i. handled (> 10 lbs.) was included to exclude replicates from studies that may have observed exposure for home gardeners and residential pest control operators, and to exclude unrepresentatively short replicates.

<u>Parameter</u>	<u>Comments</u>
Dermal grade-uncovered	All grades of studies A-E to maximize the number of replicates
Dermal grade-covered	All grades of studies A-E to maximize the number of replicates
Hand grade	All grades of studies A-E to maximize the number of replicates
Formulation-solid type	Wettable powder
Study location	Outdoor
Mixing procedure	Open
Total lbs. a.i. applied	Greater than 10.0
Exposure units	µg/pound of a.i. handled
Inhalation rate	25 L/min (PHED default)
Exposure	Combined dermal/inhalation
Head patches	Used actual and estimated head patches
Normal work clothing	Long pants, long-sleeved shirt, rubber gloves

A summary of the exposure data generated from PHED for this subset is listed in Appendix A. The following mean (arithmetic) rates of exposure per pound of a.i. mixed and loaded were computed from the subset when the workers wore long pants, long-sleeved shirt and gloves: 359 µg of dermal exposure and 69.2 µg of inhalation exposure per pound of a.i. applied. Under federal WPS, mixer/loaders handling a category III pesticide with a closed system need only wear work clothing, shoes and socks without gloves or a respirator. A survey of exposure studies indicates for mixer/loaders, the exposure to the hands can account for 50% of the total dermal exposure or 179.5 µg/lb of a.i. handled, even when chemical resistant gloves are worn (Maddy *et al.*, 1984). If this value represents approximately 10% of the exposure to the hands when a 90% protection factor for rubber gloves is used (Thongsinthusak *et al.*, 1993), then the estimated

exposure rate to the hands when gloves are not worn is 1795 µg/lb of a.i. handled (If $0.10x = 179.5 \mu\text{g/lb. a.i. handled}$, then $x = 1795 \mu\text{g/lb. a.i. handled}$). The estimated dermal exposure rate when the handlers wear only work clothing, shoes and socks is 1975 µg/lb of a.i. handled (1795 µg+ 179.5 µg/lb. a.i. handled).

The dermal and inhalation exposure values were then reduced by 95% to account for the protection provided by mixing and loading with a closed system (Thongsinthusak *et al.*, 1993). The estimated dermal and inhalation exposure incurred from mixing and loading benomyl formulated in water soluble packets are listed in Table II.

An estimate of the exposure incurred from applying benomyl with various types of application equipment was also derived from the PHED data base. One unique subset was generated for each of the listed work tasks with the following set of common selection criteria.

<u>Parameter</u>	<u>Comments</u>
Dermal grade-uncovered	All grades of studies A-E to maximize the number of replicates
Dermal grade-covered	All grades of studies A-E to maximize the number of replicates
Hand grade	All grades of studies A-E to maximize the number of replicates
Formulation-liquid	Emulsifiable concentrate or aqueous suspension or solution
Study location	Outdoor
Total lbs. a.i. applied	Greater than 10
Exposure units	µg/pound of a.i. handled
Inhalation rate	25 L/min (PHED default)
Exposure	Combined dermal/inhalation
Head patches	Used actual and estimated head patches
Normal work clothing	Long pants, long-sleeved shirt, rubber gloves

In addition each subset included one of the following parameters: orchard air blast equal to open cab; pilot-fixed-wing aerial equal to cockpit with window closed; and ground boom- ground boom tractor equal to open cab. The PHED exposure assessment was derived with the workers wearing long pants, long-sleeved shirt and gloves with the exception of the pilot who was not required to wear gloves while in the plane. The following mean rates of exposure per pound of a.i. applied were computed from the subsets: orchard air blast-204 µg of dermal exposure and 5.46 µg of inhalation exposure (Appendix B); pilot-11.9 µg of dermal exposure and 0.12 µg of inhalation exposure (Appendix C); and ground boom-135 µg of dermal exposure and 4.08 µg of inhalation exposure (Appendix D). The dermal exposure values for the arms, back, chest, head (only 50% of the value because rain hat does not protect the whole head) and legs of the orchard air blast or ground boom applicators were then reduced by 95% to account for the protection provided by the full body chemical resistant clothing (Thongsinthusak *et al.*, 1993). Inhalation exposure for the air blast and ground boom applicators was also reduced by 90% to account for the protection provided by the dust/mist filtering respirator required by the label (NIOSH, 1987). The estimates of the dermal and inhalation exposure from applying benomyl with various types of equipment are listed in Table II.

An estimate of the exposure incurred by flaggers assisting in the aerial application of benomyl with various types of aircraft was also derived from the PHED data base. One unique subset was generated for the flagger work task with the following set of selection criteria.

<u>Parameter</u>	<u>Comments</u>
Dermal grade-uncovered	All grades of studies A-E to maximize the number of replicates
Dermal grade-covered	All grades of studies A-E to maximize the number of replicates
Hand grade	All grades of studies A-E to maximize the number of replicates
Application method	Aerial: fixed wing or rotary wing
Total lb a.i. flagged	Equal to or greater than 10
Exposure units	µg/pound of a.i. handled
Inhalation rate	25 L/min (PHED default)
Exposure	Combined dermal/inhalation
Head patches	Used actual and estimated head patches
Normal work clothing	Long pants, long-sleeved shirt

A summary of the exposure data generated from PHED for this subset is listed in Appendix E. The following mean (arithmetic) rates of exposure per pound of a.i. flagged were computed from the subset when the worker wore long pants and a long-sleeved shirt: 73.6 µg of dermal exposure and 0.65 µg of inhalation exposure per pound of a.i. applied. The current Benlate® SP Fungicide label requires human flaggers to work from an enclosed cab. The dermal and inhalation exposure values were reduced by 90% to account for the protection provided by an enclosed cab without positive pressure or an air filtering system (Thongsinthusak *et al.*, 1993). Under federal WPS, workers flagging from an enclosed cab with a category III pesticide, need only wear work clothing, shoes and socks, and any respirator required by the handling work task. Since handlers are required to wear a dust/mist filtering respirator, the inhalation exposure component was reduced an additional 90% (Thongsinthusak *et al.*, 1993). The estimated dermal and inhalation exposure incurred by flaggers assisting in aerial applications of benomyl are listed in Table II.

TABLE II Estimated Daily Dermal and Inhalation Exposure From Handling Benomyl in Water Soluble Packaging

Work Task	Estimated Lbs. of A.I. Handled per Workday ^a	Dermal Exposure per Workday ^b (µg/person/day)	Inhalation Exposure per Workday ^b (µg/person/day)
Mix/Load			
air blast: stone fruit	40	3,952	138
aerial: almonds	165	16,294	571
ground boom: strawberries	10	988	34.6
Apply			
air blast: stone fruit	40	2,204	22.0
pilot: almonds	165	1,964	19.8
ground boom: strawberries	10	1,080	4.1
Mix/Load/Apply^c			
air blast: stone fruit	40	6,156	160
ground boom: strawberries	10	2,068	38.7
Flag			
almonds	165	1,214	1.16

Haskell, WH&S, 1997

^a Values are estimates for crops that represent the majority of benomyl use (DPR, 1996). The amount of a.i. handled was derived from applying benomyl at the maximum label rate for the listed crops with the following volumes of water per acre: stone fruit-125 gallons; almonds-20-30 gallons and strawberries-200 gallons. The following estimated acres treated per day represent a full workday for the indicated application method: orchard air blast-40; fixed wing aircraft-220 and ground boom in strawberries-20 (Haskell, 1998).

^b The following average exposure rates per pound of a.i. handled were used when workers mix, load and apply a pesticide formulated in a water soluble packet: a) mixing and loading - 98.8 µg of dermal and 3.46 µg of inhalation exposure; b) air blast application- 55.1 µg of dermal and 0.55 µg of inhalation exposure; c) ground boom application-108 µg of dermal and 0.41 µg of inhalation and d) aerial (fixed wing) application-11.9 µg of dermal and 0.12 µg of inhalation exposure. The estimated average rate of exposure for workers flagging an aerial application in almonds was 7.36 µg of dermal exposure and 0.007 µg of inhalation exposure per pound of a.i. applied by aircraft. See previous section for methodology. The dermal and inhalation exposure values were derived by multiplying the pounds handled per workday by the appropriate exposure rate.

^c The dermal and inhalation exposure values were derived as the sum of the exposures from mixing/loading and applying benomyl for the listed application method and crop.

II. WORKING IN TREATED CROPS: STRAWBERRIES:

The Benlate® SP Fungicide label permits a maximum of 2.5 lbs. of a.i. to be applied on strawberries per growing season. The recommended usage is to apply 0.5 lb a.i. initially

followed by 0.25 lb a.i. applications every 10-14 days for a theoretical maximum of nine applications per season. The 1992 crop of approximately 23,420 acres (University of California, 1994a) was treated with 11,442 lbs. of a.i. indicating an average of one application was made per season at the maximum label rate (DPR, 1994c). However, queries of the 1992 Pesticide Use Report data base with the PC-PUR program (PC-PUR, 1993) indicate the use of benomyl on strawberries varies according to the district and time of the season. The usage of benomyl on strawberries is limited in part by the problems inherent with its use. Resistance to some of the labeled diseases, anthracnose and common leaf spot, has been observed in the field (University of California, 1994a). Benomyl is no longer labeled for the control of Grey mold (*Botrytis*) on strawberries. The current label recommends the use on strawberries only in combination with other labeled non-benzimidazole fungicides to slow the development of resistance. Benomyl is reportedly moderately toxic to the predators and parasites utilized in IPM programs on strawberries (University of California, 1994a). The desire to maintain predator and parasite populations during critical times of the season when the buildup of pest populations can occur may curtail the use of benomyl.

The most intensive use of benomyl on strawberries during the 1992 harvest season occurred in Orange County. A crop of 1731 acres received an average of three treatments with most of the applications taking place from January through March (DPR, 1994c; PC-PUR program, 1993). The harvest season for winter plantings starts in late January-early February and lasts for approximately four months, finishing in late May (The Pink Sheet, 1996). Averaging six workdays per week with a few extra days off for bad weather, the harvest season would last approximately 100 days. For the purposes of estimating the occupational exposure to benomyl for strawberry harvesters, exposure was estimated when three consecutive applications were made 14 days apart as recommended by the Benlate[®] SP Fungicide label. With a half-life of approximately 7 days, less than 2% of the initial deposition would be expected to remain 42 days after the final Benlate[®] SP Fungicide application (Mc Nally, 1990). The estimated maximum number of workdays during the harvest season that exposure to benomyl would be expected to occur would be 28 days preceding the third sequential Benlate[®] application plus 42 days after the final application. From this total of 70 possible workdays, 10 days were subtracted to account for no harvesting on most Sundays and during bad weather.

An estimate of the dermal exposure can be made if the dislodgeable foliar residues (DFR) at the time of harvest are known and a transfer factor (dermal exposure per worker in $\mu\text{g}/\text{hour}$ divided by the DFR) can be estimated for a particular work activity. The transfer factor is an estimate of the leaf surface of the crop contacted per hour while performing the work activity.

The deposition and degradation of benomyl and MBC on the leaf surfaces of strawberries was studied by Mc Nally (1990). Three strawberry fields in Florida were sprayed at the maximum rate of 0.5 lb a.i. per acre at seven day intervals for a total of seven applications. Leaf punch samples were taken prior to the first and seventh applications, immediately following each of the seven applications, and at 1, 2, 4, 7, and 14 days after the seventh application. The samples were washed with a detergent solution to dislodge the benomyl residues and then heated to convert the benomyl to its principle metabolite, MBC. The samples were frozen and stored until analysis

with liquid chromatography. The results were expressed as the sum of the residues of benomyl and carbendazim detected.

The residue data indicated there was little accumulation of benomyl after each successive Benlate® SP Fungicide application. The half-life was estimated as seven days. A linear regression analysis of the DFR observed after the seventh application yielded the following equation: $y = -0.38967 + (-0.10751x)$ where y = natural log of $\mu\text{g}/\text{cm}^2$ and x = days (Appendix F). This equation was used to estimate the average DFR present ($0.16 \mu\text{g}/\text{cm}^2$) over a 42 day period after the last application. This value represents the average DFR present while the benomyl residues degrade through approximately six half-lives when less than 2% of the initial residues would be expected to still be present. The $0.16 \mu\text{g}/\text{cm}^2$ value was then used to estimate the average daily exposure for the strawberry harvesters during the Benlate® SP Fungicide use season. A transfer factor of $1,776 \text{ cm}^2$ of foliage contacted per hour was derived from an exposure study that observed the exposure of strawberry harvesters to captan (Edmiston *et al.*, 1990). The product of the transfer factor and the average DFR yielded an estimated $284 \mu\text{g}$ of dermal exposure per hour of work or 2.27 mg per eight-hour workday.

Although inhalation exposure to benomyl was not estimated for the strawberry harvesters, it is not likely to be a significant route of exposure. In the strawberry harvester exposure study by Holt *et al.* (1979), the respiratory component accounted for less than 0.1% of the total exposure.

The exposure to benomyl for farm workers harvesting Benlate®-treated strawberries for a single workday was observed in the study by Holt *et al.* (1979). The potential dermal and inhalation exposure was monitored for three adult females picking strawberries for two hours approximately 24 hours after a maximum label treatment of 1.0 lb of Benlate® SP Fungicide per acre. Exposure data from this study would be appropriate to use for evaluating the risk for an acute exposure from one workday. However, since the toxicological concern for benomyl arises from chronic exposure, the observations from this study are not appropriate for evaluating risk. An AADD derived from this exposure data would over-estimate the chronic occupational exposure because the value for the AADD was derived with the assumption that every harvest day of the season after the second application (60 days), was preceded with a Benlate® SP Fungicide application.

II. WORKING IN TREATED CROPS: GRAPES

The Benlate® SP Fungicide label permits a maximum of 3.0 lbs. of a.i. to be applied on grapes per growing season with 0.50-0.75 lb a.i. applied per application every 14 days for the control of Botrytis Bunch Rot. The Pesticide Use Report indicates that 33,986 acres of the 642,450 acres of grapes grown in California were treated during the 1992 growing season (DPR, 1994c). These applications were made primarily in April-June in the southern San Joaquin Valley which coincides with bloom through early berry set for grapes. The Grape Pest Management guidelines recommend leaf canopy management or a single application of a fungicide during the bloom and early fruit set to control Botrytis Bunch Rot (University of California, 1994b). Workers can start the cultural practices of bunch thinning and/or leaf removal in grapes approximately 14 days after berry set (Peacock, 1993). The dermal exposure to benomyl from performing this work activity can be estimated as the product of the DFR present when the work activity is performed and a

transfer factor that is specific for the work activity. A transfer factor of 9,000 cm² (table grapes) or 11,000 cm² (wine grapes) of foliage contacted per hour of work was used to estimate the actual dermal exposure for these cultural practices in grapes (Welsh *et al.*, 1993).

The deposition and degradation of benomyl on the leaf surfaces of grapes was studied by Powley (1989). Three sites in the San Joaquin Valley were treated with a single application of Benlate® DF Fungicide at the maximum label rate of 0.75 lb a.i. per acre. Leaf punch samples were taken prior to the application and at 1, 4, 7, 14, and 21 days after the application at each site. The samples were washed with a detergent solution to dislodge the benomyl residues and then heated to convert the benomyl to its principle metabolite, carbendazim. The samples were stored frozen until analysis with liquid chromatography. The results were expressed as the sum of the residues of benomyl and carbendazim detected. A linear regression analysis of the average DFR observed yielded the following equation: $y = -0.10276 + (-0.03974 \text{ days})$ where $y =$ natural log of $\mu\text{g}/\text{cm}^2$ and $x =$ days (Appendix G). This equation was used to estimate the average DFR present (0.36 $\mu\text{g}/\text{cm}^2$) over a 21 day work period starting 14 days after the Benlate® DF Fungicide application. With an average DFR of 0.36 $\mu\text{g}/\text{cm}^2$ present during the work period, farm workers thinning bunches and/or pulling leaves in table grapes could experience a dermal exposure of 3.24 mg (9,000 cm² X 0.36 $\mu\text{g}/\text{cm}^2$) per hour or 25.9 mg during an eight-hour workday. For wine grapes, the estimated daily dermal exposure was 31.7 mg (11,000 X 0.36 $\mu\text{g}/\text{cm}^2$ X 8 hours) per workday.

Farm workers harvesting other crops treated with benomyl can also be exposed to benomyl. Attachment One has derived estimates of the dermal exposure to workers for other hand-harvested crops that are sometimes treated with benomyl. The values in Table I of Attachment One support the observation that work tasks related to cultural practices in grapes can result in some of the greatest occupational exposures to benomyl.

The amount of exposure via the inhalation route was considered insignificant for hand labor work tasks performed in benomyl treated crops. A study by Wolfe (1976) surveyed the results from many exposure studies for workers mixing/loading and applying different pesticides with a variety of formulations. As a part of the total exposure for the worker, the inhalation component accounted for less than 1% (mean value) with a range of 0.1-3.1% for the studies reviewed. As farm workers are exposed to diluted spray residues after an application, their exposure is expected to be less.

III. NON-OCCUPATIONAL EXPOSURE FROM HOME GARDEN USES

The exposure of home owners applying home garden products that contain benomyl was estimated in earlier drafts of this exposure assessment utilizing two studies of urban applicators applying carbaryl (Gold *et al.*, 1982; Leavitt *et al.*, 1981). However, this section has been deleted from the current draft because this use pattern is expected to be discontinued in the next year or so. The trend of benomyl use in the home-garden market has been declining for several years. In the early 90's several companies had home-garden products containing benomyl. In 1996 only the Acme Division of PBI Gordon Corp. and the Green Light Company had benomyl products registered in California. Now, in 1997, only the Green Light Company's Green Light Systemic Fungicide with Benomyl, is registered in California. The product manager at the Green Light

Company has indicated the product is currently registered in California only to cover the product that may still be in the channels of trade. Du Pont Chemical is no longer selling technical benomyl that can be used for formulating home-garden products. And the Green Light Company is not manufacturing the product and does not have any left in storage. It seems appropriate to conclude that the home-garden use of benomyl will not exist in a year or two. An exposure assessment is not necessary for this use pattern.

Table III Lifetime Average Daily Dosage For Work Tasks That Involve Exposure to Benomyl

Work Task	Daily Dermal Exposure ($\mu\text{g}/\text{person}/\text{day}$)	Inhalation Exposure ($\mu\text{g}/\text{person}/\text{day}$)	Absorbed Daily Dosage ^a ($\mu\text{g}/\text{kg}/\text{day}$)	Average Annual Daily Dosage ^b ($\mu\text{g}/\text{kg}/\text{day}$)	Lifetime Average Daily Dosage ^c ($\mu\text{g}/\text{kg}/\text{day}$)
Mix/Load					
air blast-stone fruit	3,952	138	6.12	0.10	0.05
aerial-almonds	16,294	571	25.2	1.04	0.56
ground-strawberries	988	34.6	1.53	0.12	0.06
Apply					
air blast-stone fruit	2,204	22.0	3.05	0.05	0.03
aerial almonds	1,964	19.8	2.72	0.11	0.06
ground-strawberries	1,080	4.1	1.45	0.12	0.06
Mix/Load/Apply					
air blast-stone fruit	6,156	160	9.17	0.15	0.08
ground-strawberries	2,068	38.7	2.98	0.24	0.13
Flag					
	1,214	1.16	1.61	0.07	0.04
Harvest					
strawberries	2,272	not monitored	3.69	0.61	0.33
Field work-					
shoot thinning, pulling leaves (table grapes)	25,900	not monitored	42.1	2.42	1.29
(wine grapes)	31,700	not monitored	51.6	2.97	1.58

Haskell, WH&S, 1995

^a The Average Daily Dosage (ADD) was calculated with a dermal absorption rate of 10%. Inhalation absorption was considered as 50% uptake and 100% absorption (Raabe, 1988). Since the PHED exposure studies were conducted with primarily male workers, the body weight of the workers was assumed to be 75.9 kg (Thongsinthusak *et al.*, 1993). However, since farm workers can be male or female, a body weight of 61.5 kg was used to calculate the ADD for field work.

^b The Average Annual Daily Dosage (AADD) was calculated by multiplying the ADD by the estimated number of annual eight-hour workdays the task was performed and then dividing the product by 365. The annual number of workdays were estimated for the following work tasks:

1. air blast application in stone fruits-6 (Edwards, 1992).
2. aerial application in almonds-15 (50% of 30-day application season; University of California, 1985).
3. ground boom application in strawberries-29 (Haskell, 1998).
4. harvesting strawberries-60 (see text on page 13).
5. pulling grape leaves-21 (Smith, 1989).

^c The Lifetime Average Daily Dose (LADD) was calculated with the workers being exposed for 40 years with a life expectancy of 75 years (Thongsinthusak *et al.*, 1993).

Appraisal of Factors Influencing Exposure Assessment

There are several factors used to estimate occupational exposure and to calculate the Absorbed Daily Dosage that are conservative (tendency to overestimate the value of concern) in nature. These factors are real, but are typically buried in the calculations and not acknowledged. This section is an attempt to put these experimental factors in perspective with what is expected to happen in the work place.

A. Occupational exposure assessment

A common practice in pesticide exposure assessment is to measure the exposure that occurs during a few replicates of the work task and then normalize it to estimate the exposure from an eight-hour workday. Observations made in studies that varied the length of time of the replicates used to measure the exposure to pesticides observed that initially pesticide residue acquisition is at a higher rate (Spencer *et al.*, 1991; Franklin *et al.*, 1981). This higher rate is then followed by an acquisition rate that is lower and remains relatively constant for the duration of the workday. Results taken from replicates that only make observations during this initial period of greater residue acquisition will overestimate the residues acquired over an eight-hour workday. In turn, the Absorbed Daily Dosage calculated from this workday exposure will overestimate the daily dosage used to calculate the risk for an acute adverse health effect.

B. Calculations for the Absorbed Daily Dosage

To derive the Absorbed Daily Dosage, an estimate of the percent of the dermal exposure that will become bioavailable, is needed. For benomyl, this value was obtained from a rat study. Rats are used because they are relatively cheap and most of the toxicology is done with them. Also many companies have an aversion to using humans for the determination of dermal absorption, even though they are the species of choice. However, rats typically overestimate human dermal absorption by two to ten fold. This has been demonstrated in approximately a dozen different compounds tested in rats and man (Wester and Maibach, 1977, 1993; Shah and Guthrie, 1983; Sanborn, 1994; Thongsinthusak, 1994).

The deposition of pesticide residues from occupational exposure is generally uneven over the body and some regions (e.g., the hands) can constitute up to 50% of the total dermal exposure (Maddy *et al.*, 1984). The rates of dermal absorption observed in animal studies were generally inversely proportional to the amount of deposition (Wester and Maibach, 1993). However, the hands are assumed to have the same rate of absorption as the other body regions thus typically overestimating the absorbed dose. Also bioavailability of a dermal dose declines with increasing concentration (Maibach and Feldman, 1974; Shah *et al.*, 1987).

The toxic effects of pesticides are typically observed in animal studies in which the animals are dosed orally (in food or by gavage) with the pesticide in incremental doses until an effect is observed. The dose is absorbed in the gastrointestinal tract and the adverse effect occurs to the target organs only when the plasma level reaches a critical concentration. The no observed effect level (NOEL) is an estimate of the maximum dosage an organism can tolerate without manifesting the adverse effect. The NOEL divided by a factor of 10 or 100 provides an estimate of the maximum occupational exposure conventionally considered safe. Occupational exposure

to pesticides occurs primarily via the dermal route. However, dermal acquisition occurs over the entire workday and the rate of dermal absorption is slower than the oral absorption rate. A dermal dose acquired over the entire workday produces peak plasma levels at much lower levels than those from a bolus or oral feeding dosage acquired by animals in seconds to minutes (Auton *et al.*, 1993). Because the effect is highly dependent on plasma level, the net result of assuming instantaneous dermal dose acquisition and absorption is an overestimate of peak plasma concentration compared to the oral route for the same absorbed dose. To conclude that an dermal dose will have a similar toxic effect at the same lowest observed effect level (LOEL) for an orally administered dose is very conservative and typically overestimates peak plasma levels by several fold (Nolan *et al.*, 1984).

C. Conclusion

These factors are operating in the occupational exposure assessment for benomyl and as they are multiplicative, the result is significant overestimates of the Absorbed Daily Dosage for the various work tasks. A realistic upper bound estimate of exposure under normal use conditions is adequately represented by the mean estimates of exposure when all the unacknowledged conservatism built into the estimate of exposure via the dermal route are considered.

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APPENDIX A

SUMMARY STATISTICS FOR CALCULATED DERMAL AND INHALATION EXPOSURES FOR MIXER\LOADER

Exposure Scenario: Long pants, long sleeves, rubber gloves

PATCH LOCATION	DISTRIBUTION	MICROGRAMS PER LB AI SPRAYED				
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs
Head (all)	Normal	50.115	61.5956	88.6237	36.0571	32
Neck-front	Lognormal	12.9	43.3838	239.4894	11.3848	32
Neck-back	Lognormal	4.7355	29.5316	260.4705	4.3058	32
Upper arms	Lognormal	15.714	45.2591	142.1951	20.107	17
Chest	Lognormal	18.9925	57.7097	138.8205	27.4647	16
Back	Lognormal	18.9925	57.2881	140.2625	26.6824	16
Forearms	Lognormal	8.591	22.385	107.2115	13.6142	21
Thighs	Lognormal	9.55	14.3771	104.053	7.7258	11
Lower legs	Lognormal	4.76	6.9972	89.9374	5.1515	10
Feet	----	----	----	----	----	----
Hands	Lognormal	12.2678	20.4642	108.1352	11.407	20
TOTAL DERM:	189.4388	156.6183	358.9914		163.9003	
INHALATION:	Lognormal	6.8871	69.1863	196.0823	6.322	35
COMBINED:	195.7608	163.5054	428.1777		170.2223	

95% Confidence Interval on Mean: DERMAL: (-2226.3104, 2944.2932)

95% Confidence Interval on Mean: INHALATION: (0.0291, 1374.1733)

Inhalation rate: 25 Liters/minute

Number of Records: 48

Data file: MIXER\LOADER

Subset Name: WPMIXLOAD.MLOD

APPENDIX B

SUMMARY STATISTICS FOR CALCULATED DERMAL AND INHALATION EXPOSURES FOR ORCHARD AIR-BLAST APPLICATOR

Exposure Scenario: Long pants, long sleeves, rubber gloves

PATCH LOCATION	DISTRIBUTION	MICROGRAMS PER LB AI SPRAYED				
	TYPE	Median	Mean	Coef of Var	Geo, Mean	Obs
Head (all)	Lognormal	61.035	138.3778	121.2148	68.4161	18
Neck-front	Lognormal	7.9275	14.0633	116.8047	7.6855	18
Neck-back	Lognormal	11.9845	24.2251	136.3198	9.8301	18
Upper arms	Lognormal	0.873	1.067	79.6251	0.8179	15
Chest	Lognormal	1.065	3.4317	169.7584	1.5174	18
Back	Lognormal	1.065	2.2681	123.1427	1.355	18
Forearms	Lognormal	0.363	1.21	244.7355	0.4642	18
Thighs	-----	0.000	0.000	0.000	0.000	0
Lower legs	Lognormal	0.952	1.1107	24.7412	1.0898	3
Feet	Lognormal	9.301	9.17	57.8702	7.9851	3
Hands	Lognormal	1.6273	8.9272	133.5256	3.4258	18
TOTAL DERM:	102.5869	96.1933	203.8509		102.5869	
INHALATION:	Lognormal	4.7992	5.4592	77.2622	3.6497	18
COMBINED:	106.2366	100.9925	209.3101		106.2366	

95% Confidence Interval on Mean: DERMAL: (-2320.4822, 2728.184)

95% Confidence Interval on Mean: INHALATION: (0.4876, 27.3185)

Inhalation rate: 25 Liters/minute

Number of Records: 18

Data file: APPLICATOR

Subset Name: ORCHARD2.APPL

APPENDIX C

SUMMARY STATISTICS FOR CALCULATED DERMAL AND INHALATION EXPOSURES FOR PILOT

Exposure Scenario: Long pants, long sleeves, no gloves

PATCH LOCATION	DISTRIBUTION TYPE	MICROGRAMS PER LB AI SPRAYED				
		Median	Mean	Coef of Var	Geo, Mean	Obs
Head (all)	Other	0.13	0.4215	197.0344	0.2057	33
Neck-front	Other	0.015	0.0377	167.1088	0.0227	33
Neck-back	Other	0.011	0.0307	180.7818	0.0167	33
Upper arms	Other	0.291	0.3233	42.4374	0.3093	18
Chest	Other	0.355	0.355	0.000	0.355	19
Back	Other	0.355	0.355	0.000	0.355	19
Forearms	Other	0.121	0.1412	33.3569	0.1358	12
Thighs	Other	0.382	0.382	0.000	0.382	16
Lower legs	Other	0.238	0.2909	52.9048	0.2689	18
Feet	Lognormal	0.393	0.4803	88.8195	0.3311	12
Hands	Lognormal	2.025	9.0963	243.2637	1.8675	29
TOTAL DERM:	4.0966	4.316	11.9139		4.2497	
INHALATION:	Lognormal	0.0312	0.1213	205.2762	0.0338	21
COMBINED:	4.1304	4.3472	12.0352		4.2835	

95% Confidence Interval on Mean: DERMAL: (-243.0333, 266.8611)

95% Confidence Interval on Mean: INHALATION: (0.0015, 0.7624)

Inhalation rate: 25 Liters/minute

Number of Records: 33

Data file: APPLICATOR

Subset Name: AERIAL.APPL

APPENDIX D

SUMMARY STATISTICS FOR CALCULATED DERMAL AND INHALATION EXPOSURES FOR GROUND BOOM APPLICATOR

Exposure Scenario: Long pants, long sleeves, rubber gloves

PATCH LOCATION	DISTRIBUTION	MICROGRAMS PER LB AI SPRAYED				
	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs
Head (all)	Lognormal	2.21	9.841	209.7328	2.2874	60
Neck-front	Lognormal	0.255	0.8244	136.9238	0.2509	53
Neck-back	Lognormal	0.1925	0.9448	262.7223	0.1853	54
Upper arms	Lognormal	0.582	1.2368	112.5081	0.7686	16
Chest	Lognormal	2.13	6.0283	197.1601	2.0529	53
Back	Lognormal	2.13	7.3709	186.2066	2.225	38
Forearms	Lognormal	0.726	4.3664	266.982	0.847	35
Thighs	Lognormal	0.573	1.337	123.4405	0.8188	16
Lower legs	Lognormal	0.952	2.2277	138.6452	1.0661	25
Feet	Lognormal	1.048	20.3196	211.3742	1.9643	9
Hands	Lognormal	36.64	80.8191	125.2131	49.1592	11
TOTAL DERM:	61.6255	47.4385	135.316		61.6255	
INHALATION:	Other	1.2127	4.8012	182.7876	1.3293	66
COMBINED:	62.8382	48.6512	140.1172		62.9548	

95% Confidence Interval on Mean: DERMAL: (-1971.4295, 2242.0615)

95% Confidence Interval on Mean: INHALATION: (0.0444, 39.7927)

Inhalation rate: 25 Liters/minute

Number of Records: 67

Data file: APPLICATOR

Subset Name: GROUNDBOOM.APPL

APPENDIX E

SUMMARY STATISTICS FOR CALCULATED DERMAL AND INHALATION EXPOSURES FOR FLAGGER

Exposure Scenario: Long pants, long sleeves, no gloves

PATCH LOCATION	DISTRIBUTION TYPE	MICROGRAMS PER LB AI SPRAYED				
		Median	Mean	Coef of Var	Geo, Mean	Obs
Head (all)	Other	1.235	46.1817	559.396	2.5595	82
Neck-front	Other	0.1425	1.1421	220.5324	0.2143	78
Neck-back	Lognormal	0.1485	1.9619	265.4468	0.213	78
Upper arms	Other	0.582	3.0482	214.1461	0.8204	40
Chest	Other	0.355	3.2457	224.9191	0.8911	49
Back	Other	0.355	3.8036	201.496	1.0168	49
Forearms	Other	0.1815	1.3252	204.9351	0.3489	42
Thighs	Other	0.764	3.4162	314.7474	1.036	35
Lower legs	Other	0.595	2.1486	307.0371	0.6956	36
Feet	-----	0.000	0.0000	0.0000	0.0000	0
Hands	Lognormal	1.7176	7.327	155.2914	1.408	70
TOTAL DERM:	5.831	6.0761	73.6002		9.2036	
INHALATION:	Other	0.146	0.6492	193.13	0.1983	76
COMBINED:	5.977	6.2221	74.2494		9.4019	

95% Confidence Interval on Mean: DERMAL: (-1705.7874, 1852.9878)

95% Confidence Interval on Mean: INHALATION: (0.0086, 4.5811)

Inhalation rate: 25 Liters/minute

Number of Records: 92

Data file: FLAGGER

Subset Name: FLAGGER.BENOMYL

APPENDIX F

AVERAGE DISLODGEABLE FOLIAR RESIDUES OF BENOMYL DURING STRAWBERRY HARVEST SEASON

Linear regression of dislodgeable foliar residues (DFR) after three consecutive applications of Benlate on strawberries (Mc Nally, 1990)

Days	DFR	Ln of DFR	Slope	Intercept	R ²
0.1	0.64	-0.446287103	-0.10751	-0.38967	-0.9834
1	0.54	-0.616186139			
2	0.55	-0.597837001			
4	0.52	-0.653926467			
7	0.34	-1.078809661			
14	0.14	-1.966112856			

$\text{Ln}(\text{DFR}) = -0.38967 - 0.10751 \text{ days}$

Half-life = 7 days

Peak harvest season, approximately 80 days

Days After Third Application	Natural Log Value of DFR From Linear Regression	Calculated DFR in ug/cm ²
0	-0.3897	0.677
1	-0.4972	0.608
2	-0.6047	0.546
3	-0.7122	0.491
4	-0.8197	0.441
5	-0.9272	0.396
6	-1.0347	0.355
7	-1.1422	0.319
8	-1.2498	0.287
9	-1.3573	0.257
10	-1.4648	0.231
11	-1.5723	0.208
12	-1.6798	0.186
13	-1.7873	0.167
14	-1.8948	0.150
15	-2.0023	0.135
16	-2.1098	0.121
17	-2.2173	0.109
18	-2.3249	0.098
19	-2.4324	0.088
20	-2.5399	0.079
21	-2.6474	0.071
22	-2.7549	0.064
23	-2.8624	0.057
24	-2.9699	0.051

APPENDIX F (cont)

AVERAGE DISLODGEABLE FOLIAR RESIDUES OF BENOMYL DURING STRAWBERRY HARVEST SEASON

Days After Third Application	Natural Log Value of DFR From Linear Regression	Calculated DFR in ug/cm ²
25	-3.0774	0.046
26	-3.1849	0.041
27	-3.2924	0.037
28	-3.4000	0.033
29	-3.5075	0.030
30	-3.6150	0.027
31	-3.7225	0.024
32	-3.8300	0.022
33	-3.9375	0.019
34	-4.0450	0.018
35	-4.1525	0.016
36	-4.2600	0.014
37	-4.3675	0.013
38	-4.4751	0.011
39	-4.5826	0.010
40	-4.6901	0.009
41	-4.7976	0.008
42	-4.9051	0.007
Average DFR during harvest season		0.157

APPENDIX G

AVERAGE DISLODGEABLE FOLIAR RESIDUES OF BENOMYL ON GRAPES DURING MID SEASON CULTURAL PRACTICES

Linear regression of dislodgeable foliar residues (DFR) of benomyl after one maximum label treatment of Benlate on grapes (Powley, 1989).

Days	Average DFR for three treatment sites	Ln of DFR	slope	intercept	R ²
1	0.87	-0.1393	-0.03974	-0.10276	-0.99856
4	0.72	-0.3285			
7	0.61	-0.4943			
14	0.43	-0.8440			
21	0.4	-0.9163			

$\text{Ln (DFR)} = -0.10276 - 0.03974 \text{ days}$

Half-life = 18 days

Length of work season for thinning bunches,
pulling leaves = 21 days

Days After Application	Natural Log Value of DFR From Linear Regression	Calculated DFR in ug/cm ²
14	-0.6591	0.52
15	-0.6989	0.50
16	-0.7386	0.48
17	-0.7783	0.46
18	-0.8181	0.44
19	-0.8578	0.42
20	-0.8976	0.41
21	-0.9373	0.39
22	-0.9770	0.38
23	-1.0168	0.36
24	-1.0565	0.35
25	-1.0963	0.33
26	-1.1360	0.32
27	-1.1757	0.31
28	-1.2155	0.30
29	-1.2552	0.29
30	-1.2950	0.27
31	-1.3347	0.26
32	-1.3744	0.25
33	-1.4142	0.24
34	-1.4539	0.23
Average DFR during mid-season cultural practices		0.36

ATTACHMENT ONE

Farm workers working in table grapes are expected to experience some of the greatest exposures to benomyl. An estimate of their occupational exposure was included in the text and Table III of the exposure assessment for benomyl. Estimates of the dermal exposure incurred from harvesting other benomyl-treated crops are listed in the following table.

Table I Estimated Dermal Exposure to Farm Workers from Hand Harvesting Various Crops Treated with Benomyl

Crops ^a	Maximum Label Rate (lbs. a.i./acre)	Pre-harvest Interval (PHI) (days)	DFR at PHI ^b (µg/cm ²)	Transfer Factor ^c (cm ² /hour)	Dermal Exposure ^d (mg/person/day)
celery	0.25	7	0.17	1776	2.42
nectarines	1.0	3	0.91	4023	29.3
peaches	1.0	3	0.91	4023	29.3

Haskell, WH&S, 1995

^a Hand harvested crops that were reported treated with more than 10,000 lbs. of benomyl during the 1992 growing season (DPR, 1994).

^b Dislodgeable foliar residues (DFR) for various crops.

1. celery-surrogate DFR data from benomyl application on strawberries 7 days after the treatment, then divided by 2 to account for lower maximum label rate (Mc Nally, 1990).
2. nectarines and peaches-surrogate DFR data from azinphos-methyl application on plums; DFR value at one hour post application = 1.81 µg/cm² (mean value from 18 replications) (Spencer *et al.*, 1988). Multiplied by 0.67 to account for the lower application rate for benomyl and then reduced by 25% to account for the approximate degradation for a three day pre-harvest interval (7 day half-life-Mc Nally, 1990).

^c Transfer factor (cm² of foliage contacted/hour) =
$$\frac{\text{Dermal Exposure } (\mu\text{g}/\text{hour})}{\text{Dislodgeable Foliar Residue } (\mu\text{g}/\text{cm}^2)}$$

1. 1776 cm²/hour for vegetable row crop (Edmiston *et al.*, 1990).
2. 4023 cm²/hour for tree crops (see Table I of Attachment Two).

^d Dermal exposure = DFR x Transfer Factor x 8 (exposure hours per day) ÷ 1,000 µg/mg.

Table II Lifetime Average Daily Dosage For Harvest Tasks That Involve Exposure to Benomyl

Crops	Daily Dermal Exposure ^a (mg/person/day)	Inhalation Exposure (mg/person/day)	Absorbed Daily Dosage ^b (µg/kg/day)	Average Annual Daily Dosage ^c (µg/kg/day)	Lifetime Average Daily Dosage ^d (µg/kg/day)
Celery	2.42	NA	3.94	0.90	0.48
Nectarines	29.3	NA	47.6	1.44	0.77
Peaches	29.3	NA	47.6	0.78	0.42

Haskell, WH&S, 1996

NA = The amount of exposure via the inhalation route was considered insignificant for a pesticide with a low vapor pressure. A study by Wolfe (1976) surveyed the results from many exposure studies for workers mixing/loading and applying different pesticides with a variety of formulations. As a part of the total exposure for the worker, the inhalation component accounted for less than 1% (mean value) with a range of 0.1-3.1 % for the studies reviewed.

^a Values taken from column six of Table I.

^b The Average Daily Dosage (ADD) was calculated with a dermal absorption rate of 10%. Since farm workers can be male or female, a body weight of 61.5 kg was used to calculate the ADD for field work.

^c The Average Annual Daily Dosage (AADD) was calculated by multiplying the ADD by the estimated number of annual eight-hour workdays that exposure to benomyl occurred and then dividing the product by 365. The annual number of workdays were estimated for the following work tasks:

1. harvesting celery (central coast)- June-December, 143 days (USDA, 1992).
2. harvesting nectarines (southern San Joaquin Valley)- mid-May through mid-September 102 days (Calif., 1990).
3. harvesting peaches-southern San Joaquin Valley, mid-May through mid-September 102 days (Calif.,1990).

Exposure days were then estimated by multiplying the number of days in the harvest season by the percentage of the crop treated during the harvest season in a particular county.

1. celery (Monterey County) 143 days X 0.58 = 83 exposure days per season (Monterey County, 1992; DPR, 1994).
2. nectarines (Tulare County) 102 days X 0.11 = 11 exposure days per season (Calif. Fruit & Nut Acreage, 1992; DPR, 1994).
3. peaches (Tulare County) 102 days X 0.06 = 6 days (Calif. Fruit & Nut Acreage, 1992; DPR, 1994).

^d The Lifetime Average Daily Dose (LADD) was calculated with the workers being exposed for 40 years with a life expectancy of 75 years (Thongsinthusak *et al.*, 1993).

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ATTACHMENT TWO

Table I Estimation of a Generic Transfer Factor For Tree Crop Harvesters From Dermal and Dislodgeable Foliar Residue Data

Pesticide and year applied(a)	Crop and application site	No. of days post application(b)	Observed DFR ($\mu\text{g}/\text{cm}^2$)(c)	No. of workers Monitored(d)	Mean dermal exposure per harvester (mg/8 hour workday)	Transfer factor for harvesters (cm^2/hour)(e)	Total foliage contacted by all harvesters in crew (cm^2/hour)(f)
Azinphos-methyl, 1989 (1)	Peaches Sutter County	32	0.66	ten	15.6	2958	29,600
Azinphos-methyl, 1989 (1)	Peaches Sutter County	33	0.62	ten	15.5	3,119	31,200
Azinphos-methyl, 1990 (1)	Peaches Sutter County	52	0.36	eleven	12.0	4,174	45,900
Azinphos-methyl, 1990 (1)	Peaches Sutter County	53	0.61	eleven	14.0	2,877	31,600
Azinphos-methyl, 1989 (1)	Peaches Stanislaus County	60	0.009	eight	0.44	6,111	48,900
Azinphos-methyl, 1989 (1)	Peaches Stanislaus County	61	0.011	nine	1.25	14,205	127,800
Azinphos-methyl, 1989 (1)	Peaches Stanislaus County	62	0.07	eight	4.30	7,679	61,400
Phosmet 1989 (1)	Peaches Stanislaus County	34	2.5	eight	28.17	1,409	11,300
Phosmet 1989 (1)	Peaches Stanislaus County	35	2.5	eight	31.6	1,579	14,200
Phosmet 1989 (1)	Peaches Stanislaus County	36	2.5	eight	39.3	1,964	15,700
Phosalone 1976 (2,3)	Peaches Stanislaus County	13-15	2.90	six (5)	76.0	3,276	19,700
Phosalone 1977 (2,3)	Peaches Stanislaus County	7-9	3.59	six (5)	67.2	2,340	14,000
Phosalone 1977 (2,3)	Peaches Stanislaus County	22-24	0.90	six (5)	57.2	7,944	47,700

Table I(cont) Estimation of a Generic Transfer Factor For Tree Crop Harvesters From Dermal Exposure and Dislodgeable Foliar Residue Data

Pesticide and year applied(a)	Crop and application site	No. of days post application(b)	Observed DFR ($\mu\text{g}/\text{cm}^2$)(c)	No. of workers Monitored(d)	Mean dermal exposure per harvester (mg/8 hour workday)	Transfer factor for harvesters (cm^2/hour)(e)	Total foliage contacted by all harvesters in crew (cm^2/hour)(f)
Phosalone 1977 (2,3)	Peaches Stanislaus County	3-5	2.89	six (5)	111	4,810	28,900
Azinphos-methyl 1976 (2,3)	Peaches Stanislaus County	22-24	0.20	six (5)	12.3	7,689	46,100
Propargite 1988 (4)	Peaches Fresno County	34	0.59	ten	5.17	1,095	11,000
Propargite 1988 (4)	Peaches Fresno County	39	0.54	ten	5.55	1,285	12,900
Propargite 1988 (4)	Peaches Fresno County	45	0.48	ten	3.65	950	9,500

**Weighted Mean Transfer Factor for all Data = Sum of Total Foliage Contacted by All Harvesters in Each Study divided by the Total Number of Workers Monitored in All Studies.
= 4023 $\mu\text{g}^2/\text{hour}$**

(a) Sources of data.

- (1) Spencer et al., 1993.
- (2) Pependorf et al., 1979.
- (3) Pependorf and Leffingwell, 1982.
- (4) Rech, 1989.

(b) The number of days after the pesticide application when the dislodgeable foliar residue samples were taken.

(c) DFR = Dislodgeable Foliar Residues. The DFR reported in Pependorf and Leffingwell (1982) were divided by 2 to calculate the DFR for both sides of the leaf.

(d) The number of harvesters monitored for dermal exposure with patch dosimetry for a 4-8 hour exposure period per workday.

(5) Each worker (ten total) only wore two patches and the patches were pooled at the end of workday to approximate the total dermal exposure for two workers. Therefore, each harvest day was considered two workdays.

(e) Formula for calculating Transfer Factor:

Mg of dermal exposure per workday X 1,000 $\mu\text{g}/\text{mg}$ divided by observed DFR X 8 hr/day.

(f) Calculated by multiplying the number of workers monitored by the transfer factor.

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APPENDIX C
CANCER MODELING

Appendix C Cancer modeling

DATE: 09/30/1997

TIME: 10:51:19

GLOBAL 86 (MAY 1986)

BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM

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(318) 255-4800

Benomyl; F mice; hepatocellular tumors

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	4/ 64	5.71
2	75.0000	9/ 60	6.96
3	225.000	13/ 73	12.20
4	750.000	21/ 68	22.03

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 1.3742

P-VALUE FOR THE MONTE CARLO TEST IS .3600000000

FORM OF PROBABILITY FUNCTION:

$P(\text{DOSE}) = 1 - \exp(-Q_0 - Q_1 * D - Q_2 * D^2)$

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = 9.347089272686E-02
Q(1) = 3.975099826745E-04
Q(2) = .000000000000

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -117.250192979

CALCULATIONS ARE BASED UPON EXTRA RISK
 LINEARIZED MULTISTAGE CONFIDENCE LIMITS

RISK -----	MLE DOSE -----	LOWER BOUND ON DOSE -----	UPPER BOUND ON RISK -----	CONFIDENCE LIMIT SIZE -----
.10000	265.05	186.45	.13910	90.0
		171.17	.15054	95.0
		159.54	.16057	97.5
		147.61	.17237	99.0
1.00000E-02	25.283	17.786	1.41856E-02	90.0
		16.328	1.54425E-02	95.0
		15.219	1.65581E-02	97.5
		14.080	1.78853E-02	99.0
1.00000E-03	2.5169	1.7705	1.42126E-03	90.0
		1.6254	1.54807E-03	95.0
		1.5150	1.66076E-03	97.5
		1.4017	1.79496E-03	99.0
1.00000E-04	.25158	.17697	1.42153E-04	90.0
		.16247	1.54846E-04	95.0
		.15143	1.66126E-04	97.5
		.14010	1.79560E-04	99.0
1.00000E-05	2.51567E-02	1.76966E-02	1.42156E-05	90.0
		1.62459E-02	1.54849E-05	95.0
		1.51427E-02	1.66130E-05	97.5
		1.40096E-02	1.79567E-05	99.0
1.00000E-06	2.51566E-03	1.76965E-03	1.42156E-06	90.0
		1.62458E-03	1.54850E-06	95.0
		1.51426E-03	1.66131E-06	97.5
		1.40096E-03	1.79567E-06	99.0
1.00000E-07	2.51566E-04	1.76965E-04	1.42156E-07	90.0
		1.62458E-04	1.54850E-07	95.0
		1.51426E-04	1.66131E-07	97.5
		1.40096E-04	1.79568E-07	99.0
1.00000E-08	2.51566E-05	1.76965E-05	1.42156E-08	90.0
		1.62458E-05	1.54850E-08	95.0
		1.51426E-05	1.66131E-08	97.5
		1.40095E-05	1.79568E-08	99.0

END OF LINEARIZED MULTISTAGE CONFIDENCE LIMITS

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
----	-----	-----	-----	-----
1.00000E-05	2.51567E-02	1.62459E-02	95.0%	Q(0) = 6.80071E-02 Q(1) = 6.15544E-04 Q(2) = .00000
1.00000E-06	2.51566E-03	1.62458E-03	95.0%	Q(0) = 6.80071E-02 Q(1) = 6.15544E-04 Q(2) = .00000

GLOBAL 86 UPPER CONFIDENCE LIMITS ON RISK FOR FIXED DOSE

DOSE	MLE RISK	UPPER BOUND ON RISK	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
----	-----	-----	-----	-----
3.0000	1.19182E-03	1.84493E-03	95.0%	Q(0) = 6.80071E-02 Q(1) = 6.15544E-04 Q(2) = .00000
5.00000E-08	1.98755E-11	3.07770E-11	95.0%	Q(0) = 6.80075E-02 Q(1) = 6.15539E-04 Q(2) = .00000

NORMAL COMPLETION!

APPENDIX D

COMMODITY RESIDUE VALUES

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration

RESIDUE FILE NAME: BENMYLCP

ANALYSIS DATE: 08-03-1999

NFCS Combined 89-92 DATA

EPA Reference dose (RfD, chronic) = 0.050000 mg/kg body-wt/day

DPR NOEL (Chronic) = 15.000000 mg/kg body-wt/day

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. PCT adjustments made.

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
1	N	BLACKBERRIES	0.230000	1.00	1.00	FDAsur
2	N	BOYSENBERRIES	0.230000	1.00	1.00	FDAsur
3	N	DEWBERRIES	0.230000	1.00	1.00	FDAsur
4	N	LOGANBERRIES	0.230000	1.00	1.00	FDAsur
5	N	RASPBERRIES	0.120000	1.00	1.00	FDA
7	N	BLUEBERRIES	0.230000	1.00	1.00	FDA
10	N	CURRANTS	0.230000	1.00	1.00	FDAsur
13	N	GRAPES	0.016000	1.00	1.00	DPR
14	N	GRAPES-RAISINS	0.025000	1.00	1.00	FDA
15	N	GRAPES-JUICE	0.025000	1.00	1.00	FDA
17	N	STRAWBERRIES	0.120000	1.00	1.00	DPR
20	K	CITRUS CITRON	0.440000	1.00	1.00	FDAsur
22	K	GRAPEFRUIT-PEELED FRUIT	0.180000	1.00	1.00	FDA
23	K	GRAPEFRUIT-JUICE	0.180000	2.10	1.00	FDA
24	K	KUMQUATS	0.440000	1.00	1.00	FDAsur
26	K	LEMONS-PEELED FRUIT	0.440000	1.00	1.00	FDA
27	K	LEMONS-PEEL	0.440000	1.00	1.00	FDA
28	K	LEMONS-JUICE	0.440000	2.00	1.00	FDA
30	K	LIMES-PEELED FRUIT	0.025000	1.00	1.00	FDA-GP
31	K	LIMES-PEEL	0.025000	1.00	1.00	FDA-GP
32	K	LIMES-JUICE	0.025000	2.00	1.00	FDA-GP
33	K	ORANGES-JUICE-CONCENTRATE	0.025000	1.00	1.00	FDA-GP
34	K	ORANGES-PEELED FRUIT	0.025000	1.00	1.00	FDA-GP
35	K	ORANGES-PEEL	0.025000	1.00	1.00	FDA-GP
36	K	ORANGES-JUICE	0.025000	1.00	1.00	FDA-GP
37	K	TANGELOS	0.180000	1.00	1.00	FDAsur
38	K	TANGERINES	0.180000	1.00	1.00	FDAsur
39	K	TANGERINES-JUICE	0.180000	2.30	1.00	FDAsur
40	R	ALMONDS	0.050000	1.00	1.00	REGsur
44	R	FILBERTS (HAZELNUTS)	0.050000	1.00	1.00	REGsur
46	R	MACADAMIA NUTS (BUSH NUTS)	0.050000	1.00	1.00	REG
47	R	PECANS	0.050000	1.00	0.10	REGsur
48	R	WALNUTS	0.050000	1.00	1.00	REGsur
50	A	PISTACHIO NUTS	0.025000	1.00	1.00	REG
52	L	APPLES	0.040000	1.00	1.00	FDA-GP
53	L	APPLES-DRIED	0.040000	8.00	1.00	FDA-GP
54	L	APPLES-JUICE/CIDER	0.025000	1.00	1.00	FDA-GP
56	L	PEARS	0.025000	1.00	1.00	FDA-GP

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
57	L	PEARS-DRIED	0.025000	6.25	1.00	FDA-GP
59	M	APRICOTS	0.058000	1.00	1.00	FDA
60	M	APRICOTS-DRIED	0.058000	6.00	1.00	FDA
61	M	CHERRIES	0.052000	1.00	1.00	FDA
62	M	CHERRIES-DRIED	0.052000	4.00	1.00	FDA
63	M	CHERRIES-JUICE	0.052000	1.50	1.00	FDA
64	M	NECTARINES	0.058000	1.00	1.00	FDA
65	M	PEACHES	0.140000	1.00	1.00	FDA
66	M	PEACHES-DRIED	0.140000	7.00	1.00	FDA
67	M	PLUMS (DAMSONS)	0.083000	1.00	1.00	FDA
68	M	PLUMS-PRUNES (DRIED)	0.025000	1.00	1.00	FDA
69	M	PLUMS/PRUNE-JUICE	0.025000	1.40	1.00	FDA
72	A	BANANAS	0.025000	1.00	1.00	PDP
73	A	BANANAS-DRIED	0.025000	3.90	1.00	PDP
80	A	MANGOES	0.025000	1.00	1.00	FDA
89	A	PINEAPPLES-PEELED FRUIT	0.270000	1.00	1.00	FDA
90	A	PINEAPPLES-DRIED	0.270000	5.00	1.00	FDA
91	A	PINEAPPLES-JUICE	0.270000	1.70	1.00	FDA
141	J	CANTALOUPE-NECTAR	0.025000	1.00	1.00	DPR
142	J	CANTALOUPE-PULP (MUSKMELON)	0.025000	1.00	1.00	DPR
143	J	CASABAS	0.220000	1.00	1.00	REGsur
144	J	CRENSHAW	0.220000	1.00	1.00	REGsur
145	J	HONEYDEW MELONS	0.220000	1.00	1.00	REGsur
146	J	PERSIAN MELONS	0.220000	1.00	1.00	REGsur
147	J	WATERMELON	0.130000	1.00	0.25	REG
148	J	CUCUMBERS	0.140000	1.00	1.00	DPR
149	J	PUMPKIN	0.500000	1.00	1.00	REGsur
150	J	SQUASH-SUMMER	0.500000	1.00	1.00	REG
151	J	SQUASH-WINTER	0.500000	1.00	1.00	REGsur
154	I	EGGPLANT	0.016000	1.00	1.00	REG
155	I	PEPPERS-SWEET (GARDEN)	0.021000	1.00	1.00	REG
156	I	CHILI PEPPERS (JALAPENO)	0.021000	1.00	1.00	REG
159	I	TOMATOES-WHOLE	2.750000	0.18	0.10	REG
160	I	TOMATOES-JUICE	0.400000	1.00	0.10	REGprc
161	I	TOMATOES-PUREE	0.025000	1.00	1.00	FDA-GP
162	I	TOMATOES-PASTE	0.025000	1.00	1.00	FDA-GP
163	I	TOMATOES-CATSUP	0.070000	1.00	0.10	REGprc
166	E	CELERY	0.060000	1.00	1.00	DPR
168	F	BROCCOLI	0.025000	1.00	1.00	PDP
169	F	BRUSSELS SPROUTS	3.770000	1.00	1.00	REG
170	F	CABBAGE-GREEN AND RED	0.200000	1.00	1.00	REGsur
171	F	CAULIFLOWER	0.200000	1.00	1.00	EPA
172	F	COLLARDS	0.043000	1.00	1.00	REG
173	F	CABBAGE-CHINESE/CELERY/BOK CHO	0.200000	1.00	1.00	REG
174	F	KALE	0.200000	1.00	1.00	EPA
175	F	KOHLRABI	0.200000	1.00	1.00	EPA
183	F	MUSTARD GREENS	0.009000	1.00	1.00	REG
186	E	SPINACH	0.050000	1.00	1.00	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
198	B	CARROTS	0.086000	1.00	1.00	REG
202	D	GARLIC	0.200000	1.00	1.00	EPA
214	B	RUTABAGAS-ROOTS	0.022000	1.00	1.00	REG
218	B	SWEET POTATOES (INCLUDING YAMS	0.025000	1.00	1.00	DPR
219	B	TURNIPS-ROOTS	0.022000	1.00	1.00	REG
227	G	BEANS-DRY-GREAT NORTHERN	0.050000	1.00	1.00	REG
228	G	BEANS-DRY-KIDNEY	0.050000	1.00	1.00	REG
229	G	BEANS-DRY-LIMA	0.050000	1.00	1.00	REG
230	G	BEANS-DRY-NAVY (PEA)	0.050000	1.00	1.00	REG
231	G	BEANS-DRY-OTHER	0.050000	1.00	1.00	REG
232	G	BEANS-DRY-PINTO	0.050000	1.00	1.00	REG
233	G	BEANS-SUCCULENT-LIMA	0.040000	1.00	1.00	PDPsur
234	G	BEANS-SUCCULENT-GREEN	0.040000	1.00	1.00	PDP
235	G	BEANS-SUCCULENT-OTHER	0.040000	1.00	1.00	PDP
236	G	BEANS-SUCCULENT-YELLOW/WAX	0.040000	1.00	1.00	PDPsur
238	O	CORN/SWEET	0.025000	1.00	1.00	FDA
239	A	PEANUTS-WHOLE	0.050000	1.00	1.00	REG
249	G	BEANS-DRY-BROADBEANS	0.050000	1.00	1.00	REG
250	G	BEANS-SUCCULENT-BROADBEANS	0.040000	1.00	1.00	PDPsur
251	G	BEANS-DRY-PIGEON BEANS	0.050000	1.00	1.00	REG
253	G	BEANS-UNSPECIFIED	0.050000	1.00	1.00	REG
256	G	BEANS-DRY-HYACINTH	0.050000	1.00	1.00	REG
257	G	BEANS-SUCCULENT-HYACINTH	0.040000	1.00	1.00	PDPsur
258	G	BEANS-DRY-BLACKEYE PEAS/COWPEA	0.050000	1.00	1.00	REG
259	G	BEANS-DRY-GARBANZO/CHICK PEA	0.050000	1.00	1.00	REG
261	A	MUSHROOMS	0.040000	1.00	1.00	FDA
265	O	BARLEY	0.050000	1.00	1.00	REG
266	O	CORN/GRAIN-ENDOSPERM	0.025000	1.00	1.00	FDA
267	O	CORN/GRAIN-BRAN	0.025000	1.00	1.00	FDA
268	O	CORN SUGAR	0.025000	1.50	1.00	FDA
269	O	OATS	0.025000	1.00	1.00	REG
270	O	RICE-ROUGH (BROWN)	0.110000	0.01	0.20	REG
271	O	RICE-MILLED (WHITE)	0.110000	0.01	0.20	REG
272	O	RYE-ROUGH	0.025000	1.00	1.00	REGsur
273	O	RYE-GERM	0.025000	1.00	1.00	REGsur
274	O	RYE-FLOUR	0.025000	1.00	1.00	REGsur
276	O	WHEAT-ROUGH	0.025000	1.00	1.00	REG
277	O	WHEAT-GERM	0.025000	1.00	1.00	REGprc
278	O	WHEAT-BRAN	0.025000	1.00	1.00	REGprc
279	O	WHEAT-FLOUR	0.025000	1.00	1.00	REGprc
282	B	BEET SUGAR	0.050000	1.00	1.00	REG
289	O	CORN GRAIN-OIL	0.050000	1.00	1.00	FDA
293	A	PEANUTS-OIL	0.050000	1.00	1.00	REG
297	G	SOYBEANS-OIL	0.025000	1.00	0.01	REG
304	G	SOYBEANS-MATURE SEEDS DRY	0.025000	1.00	0.01	REG
305	G	SOYBEANS-FLOUR (FULL FAT)	0.025000	1.00	0.01	REG
306	G	SOYBEANS-FLOUR (LOW FAT)	0.025000	1.00	0.01	REG
307	G	SOYBEANS-FLOUR (DEFATTED)	0.025000	1.00	0.01	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
315	A	GRAPES-WINE AND SHERRY	0.016000	1.00	1.00	DPR
318	X	MILK-NONFAT SOLIDS	0.001200	1.00	1.00	REGTAS
319	X	MILK-FAT SOLIDS	0.005800	1.00	1.00	REGTAS
320	X	MILK SUGAR (LACTOSE)	0.002600	1.00	1.00	REGTAS
321	U	BEEF-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
322	U	BEEF(ORGAN MEATS)-OTHER	0.075000	1.00	1.00	REGTAS
323	U	BEEF-DRIED	0.000400	1.92	1.00	REGTAS
324	U	BEEF(BONELESS)-FAT	0.000700	1.00	1.00	REGTAS
325	U	BEEF(ORGAN MEATS)-KIDNEY	0.004500	1.00	1.00	REGTAS
326	U	BEEF(ORGAN MEATS)-LIVER	0.007500	1.00	1.00	REGTAS
327	U	BEEF(BONELESS)-LEAN (FAT/FREE)	0.000400	1.00	1.00	REGTAS
328	U	GOAT-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
329	U	GOAT(ORGAN MEATS)-OTHER	0.075000	1.00	1.00	REGTAS
330	U	GOAT(BONELESS)-FAT	0.000700	1.00	1.00	REGTAS
331	U	GOAT(ORGAN MEATS)-KIDNEY	0.004500	1.00	1.00	REGTAS
332	U	GOAT(ORGAN MEATS)-LIVER	0.075000	1.00	1.00	REGTAS
333	U	GOAT(BONELESS)-LEAN (FAT/FREE)	0.000400	1.00	1.00	REGTAS
334	U	HORSE	0.000400	1.00	1.00	REGTAS
336	U	SHEEP-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
337	U	SHEEP(ORGAN MEATS)-OTHER	0.075000	1.00	1.00	REGTAS
338	U	SHEEP(BONELESS)-FAT	0.000700	1.00	1.00	REGTAS
339	U	SHEEP(ORGAN MEATS)-KIDNEY	0.004500	1.00	1.00	REGTAS
340	U	SHEEP(ORGAN MEATS)-LIVER	0.075000	1.00	1.00	REGTAS
341	U	SHEEP(BONELESS)-LEAN (FAT FREE)	0.000400	1.00	1.00	REGTAS
342	U	PORK-MEAT BYPRODUCTS	0.013000	1.00	1.00	REGTAS
343	U	PORK(ORGAN MEATS)-OTHER	0.013000	1.00	1.00	REGTAS
344	U	PORK(BONELESS)-FAT	0.000100	1.00	1.00	REGTAS
345	U	PORK(ORGAN MEATS)-KIDNEY	0.000800	1.00	1.00	REGTAS
346	U	PORK(ORGAN MEATS)-LIVER	0.013000	1.00	1.00	REGTAS
347	U	PORK(BONELESS)-LEAN (FAT FREE)	0.000100	1.00	1.00	REGTAS
355	V	TURKEY-BYPRODUCTS	0.002100	1.00	1.00	REGTAS
356	V	TURKEY-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
357	V	TURKEY-(BONELESS)-FAT	0.002100	1.00	1.00	REGTAS
358	V	TURKEY-(BONELESS)LEAN/FAT FREE	0.000050	1.00	1.00	REGTAS
359	V	TURKEY-UNSPECIFIED	0.002100	1.00	1.00	REGTAS
360	V	POULTRY-OTHER-LEAN (FAT FREE)	0.000050	1.00	1.00	REGTAS
361	V	POULTRY-OTHER-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
362	V	POULTRY-OTHER-FAT	0.002100	1.00	1.00	REGTAS
363	X	EGGS-WHOLE	0.002000	1.00	1.00	REGTAS
364	X	EGGS-WHITE ONLY	0.002000	1.00	1.00	REGTAS
365	X	EGGS-YOLK ONLY	0.002000	1.00	1.00	REGTAS
366	V	CHICKEN-BYPRODUCTS	0.002100	1.00	1.00	REGTAS
367	V	CHICKEN-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
368	V	CHICKEN (BONELESS)-FAT	0.002100	1.00	1.00	REGTAS
369	V	CHICKEN(BONELESS)LEAN/FAT FREE	0.000050	1.00	1.00	REGTAS
377	L	APPLES-JUICE-CONCENTRATE	0.025000	1.00	1.00	FDA-GP
378	A	BANANAS-NECTAR	0.025000	1.00	1.00	PDP
379	B	BEEET SUGAR-MOLASSES	0.050000	1.00	1.00	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
380	N	BLACKBERRIES-JUICE	0.230000	1.00	1.00	FDAsur
383	F	CABBAGE-SAVOY	0.200000	1.00	1.00	EPA
384	E	CELERY JUICE	0.060000	1.00	1.00	DPR
385	V	CHICKEN-GIBLETS (EXCL. LIVER)	0.002100	1.00	1.00	REGTAS
388	O	CORN SUGAR-MOLASSES	0.025000	1.50	1.00	FDA
392	N	GRAPES-JUICE-CONCENTRATE	0.025000	1.00	1.00	FDA-GP
398	X	MILK-BASED WATER	0.001200	1.00	1.00	REGTAS
399	O	OATS-BRAN	0.025000	1.00	1.00	REG
402	M	PEACHES-JUICE	0.140000	1.00	1.00	FDA
403	A	PEANUT-BUTTER	0.050000	1.89	1.00	REG
404	L	PEARS-NECTAR	0.025000	1.00	1.00	FDA-GP
406	A	PINEAPPLES-JUICE-CONCENTRATE	0.270000	1.00	1.00	FDA
408	O	RICE-BRAN	0.110000	0.01	0.20	REG
409	O	RICE-WILD	0.110000	0.01	0.20	REG
410	M	APRICOT JUICE OR NECTAR	0.058000	1.00	1.00	FDA
416	N	STRAWBERRIES-JUICE	0.120000	1.00	1.00	DPR
420	K	TANGERINES-JUICE-CONCENTRATE	0.180000	7.35	1.00	FDAsur
423	I	TOMATOES-DRIED	2.750000	2.57	0.10	REG
424	U	VEAL- (BONELESS) -FAT	0.000700	1.00	1.00	REGTAS
425	U	VEAL- (BONELESS) -LEAN (FAT FREE	0.000400	1.00	1.00	REGTAS
426	U	VEAL- (ORGAN MEATS) -KIDNEY	0.004500	1.00	1.00	REGTAS
427	U	VEAL- (ORGAN MEATS) -LIVER	0.075000	1.00	1.00	REGTAS
428	U	VEAL- (ORGAN MEATS) -OTHER	0.075000	1.00	1.00	REGTAS
429	U	VEAL-DRIED	0.000400	1.92	1.00	REGTAS
430	U	VEAL-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
436	J	WATERMELON-JUICE	0.130000	1.00	1.00	REG
437	O	WHEAT-GERM OIL	0.025000	1.00	1.00	REGprc
441	K	GRAPEFRUIT-JUICE-CONCENTRATE	0.180000	8.26	1.00	FDA
442	K	LEMONS-JUICE-CONCENTRATE	0.440000	11.40	1.00	FDA
443	K	LIMES-JUICE-CONCENTRATE	0.025000	6.00	1.00	FDA
448	K	GRAPEFRUIT PEEL	0.180000	1.00	1.00	FDA
449	V	TURKEY- (ORGAN MEATS) -OTHER	0.002100	1.00	1.00	REGTAS
940	A	PEANUTS HULLED	0.050000	1.00	1.00	REG

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration

RESIDUE FILE NAME: BENMYLCP

ANALYSIS DATE: 08-03-1999

NFCS Combined 89-92 DATA

EPA Reference dose (RfD, chronic) = 0.050000 mg/kg body-wt/day

DPR NOEL (Chronic) = 15.000000 mg/kg body-wt/day

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. PCT adjustments made.

 TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE		
	mg/kg body-wt/day	Margin of Exposure 1/	Percent of RfD
U.S. POP - 48 STATES - ALL SEASONS	0.000447	33,537	0.9%
U.S. POPULATION - SPRING SEASON	0.000436	34,440	0.9%
U.S. POPULATION - SUMMER SEASON	0.000451	33,289	0.9%
U.S. POPULATION - AUTUMN SEASON	0.000458	32,747	0.9%
U.S. POPULATION - WINTER SEASON	0.000444	33,816	0.9%
NORTHEAST REGION	0.000507	29,607	1.0%
MIDWEST REGION	0.000393	38,191	0.8%
SOUTHERN REGION	0.000417	35,947	0.8%
WESTERN REGION	0.000503	29,812	1.0%
PACIFIC REGION	0.000507	29,593	1.0%
HISPANICS	0.000397	37,751	0.8%
NON-HISPANIC WHITES	0.000451	33,237	0.9%
NON-HISPANIC BLACKS	0.000433	34,666	0.9%
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.000560	26,790	1.1%
ALL INFANTS	0.001035	14,493	2.1%
NURSING INFANTS (<1 YEAR OLD)	0.000493	30,445	1.0%
NON-NURSING INFANTS (<1 YEAR OLD)	0.001263	11,874	2.5%
CHILDREN (1-6 YEARS)	0.000914	16,404	1.8%
CHILDREN (7-12 YEARS)	0.000606	24,765	1.2%
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.000334	44,865	0.7%
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.000383	39,161	0.8%
FEMALES (13-50 YEARS)	0.000343	43,682	0.7%
FEMALES (13+/PREGNANT/NOT NURSING)	0.000321	46,665	0.6%
FEMALES (13+/NURSING)	0.000608	24,671	1.2%
MALES (13-19 YEARS)	0.000324	46,357	0.6%
MALES (20+ YEARS)	0.000348	43,059	0.7%
SENIORS (55+)	0.000437	34,312	0.9%

 1. Margin of Exposure = DPR NOEL / Dietary Exposure

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration

RESIDUE FILE NAME: BENMYLCP

ANALYSIS DATE: 08-03-1999

NFCS Combined 89-92 DATA

Q* = 0.004300

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. PCT adjustments made.

TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE	
	mg/kg body-wt/day	Life-Time Risk (Q* = 0.004300)
U.S. POP - 48 STATES - ALL SEASONS	0.000447	1.92E-06
U.S. POPULATION - SPRING SEASON	0.000436	1.87E-06
U.S. POPULATION - SUMMER SEASON	0.000451	1.94E-06
U.S. POPULATION - AUTUMN SEASON	0.000458	1.97E-06
U.S. POPULATION - WINTER SEASON	0.000444	1.91E-06
NORTHEAST REGION	0.000507	2.18E-06
MIDWEST REGION	0.000393	1.69E-06
SOUTHERN REGION	0.000417	1.79E-06
WESTERN REGION	0.000503	2.16E-06
PACIFIC REGION	0.000507	2.18E-06
HISPANICS	0.000397	1.71E-06
NON-HISPANIC WHITES	0.000451	1.94E-06
NON-HISPANIC BLACKS	0.000433	1.86E-06
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.000560	2.41E-06
ALL INFANTS	0.001035	4.45E-06
NURSING INFANTS (<1 YEAR OLD)	0.000493	2.12E-06
NON-NURSING INFANTS (<1 YEAR OLD)	0.001263	5.43E-06
CHILDREN (1-6 YEARS)	0.000914	3.93E-06
CHILDREN (7-12 YEARS)	0.000606	2.60E-06
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.000334	1.44E-06
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.000383	1.65E-06
FEMALES (13-50 YEARS)	0.000343	1.48E-06
FEMALES (13+/PREGNANT/NOT NURSING)	0.000321	1.38E-06
FEMALES (13+/NURSING)	0.000608	2.61E-06
MALES (13-19 YEARS)	0.000324	1.39E-06
MALES (20+ YEARS)	0.000348	1.50E-06
SENIORS (55+)	0.000437	1.88E-06

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration
ANALYSIS DATE: 08-03-1999

RESIDUE FILE NAME: BENMYLCP

NFCS Combined 89-92 DATA

Q* = 0.006700

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. PCT adjustments made.

TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE	
	mg/kg body-wt/day	Life-Time Risk (Q* = 0.006700)
U.S. POP - 48 STATES - ALL SEASONS	0.000447	3.00E-06
U.S. POPULATION - SPRING SEASON	0.000436	2.92E-06
U.S. POPULATION - SUMMER SEASON	0.000451	3.02E-06
U.S. POPULATION - AUTUMN SEASON	0.000458	3.07E-06
U.S. POPULATION - WINTER SEASON	0.000444	2.97E-06
NORTHEAST REGION	0.000507	3.39E-06
MIDWEST REGION	0.000393	2.63E-06
SOUTHERN REGION	0.000417	2.80E-06
WESTERN REGION	0.000503	3.37E-06
PACIFIC REGION	0.000507	3.40E-06
HISPANICS	0.000397	2.66E-06
NON-HISPANIC WHITES	0.000451	3.02E-06
NON-HISPANIC BLACKS	0.000433	2.90E-06
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.000560	3.75E-06
ALL INFANTS	0.001035	6.93E-06
NURSING INFANTS (<1 YEAR OLD)	0.000493	3.30E-06
NON-NURSING INFANTS (<1 YEAR OLD)	0.001263	8.46E-06
CHILDREN (1-6 YEARS)	0.000914	6.13E-06
CHILDREN (7-12 YEARS)	0.000606	4.06E-06
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.000334	2.24E-06
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.000383	2.57E-06
FEMALES (13-50 YEARS)	0.000343	2.30E-06
FEMALES (13+/PREGNANT/NOT NURSING)	0.000321	2.15E-06
FEMALES (13+/NURSING)	0.000608	4.07E-06
MALES (13-19 YEARS)	0.000324	2.17E-06
MALES (20+ YEARS)	0.000348	2.33E-06
SENIORS (55+)	0.000437	2.93E-06

APPENDIX E

DIETARY RISK ASSESSMENT

BENOMYL (Benlate ®)

DIETARY EXPOSURE ASSESSMENT SUMMARY

Wesley C. Carr, Jr.

HEALTH ASSESSMENT SECTION
MEDICAL TOXICOLOGY BRANCH
CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

August 6, 1999

I. Summary

Acute and chronic dietary exposures along with an acute tolerance assessment were performed for the pesticide benomyl. A NOEL (No Observed Effect Level) of 15.0 mg/kg/day was used for the acute dietary analysis and the tolerance assessment. The value of 15.0 mg/kg/day, benomyl NOEL, was used for the chronic non-oncogenic analysis. The maximum likelihood value of 0.0043 (mg/kg/day)⁻¹ and the upper bound value of 0.0067 (mg/kg/day)⁻¹ were used to estimate human cancer potency in the lifetime oncogenic analysis. Over 80 Raw Agricultural Commodities (RACs) and crop group residues were assessed. The residue data were derived from registrant supplied field trial data, DPR, FDA, and USDA PDP programs monitoring data or U.S. EPA tolerances (Table 1).

Exposures were calculated for one acute dietary intake using the combined RACs residue values. The acute dietary scenario was evaluated using the acute endpoint NOEL value based on female rabbit reproductive effects. The acute exposure values ranged from 0.010010 mg/kg/day, females 13 + years (pregnant, not nursing) to 0.038567, nursing infants < 1 year (Table 2).

Exposures were calculated for two chronic dietary intakes using the combined RACs. Both dietary scenarios were evaluated using the chronic endpoint NOEL value of 15.0 mg/kg/day based on dog hepatotoxicity effects. The first scenario consisted of dietary exposure residue data without the inclusion of percent of the crop treated (PCT) and processing information. The second chronic dietary exposure analysis used crop adjustment factors to reflect national percentages (<100%) of the crop treated with benomyl for several different commodities. Six commodities were adjusted; pecan, rice, soybean, fresh tomatoes, processing tomatoes, and watermelons. The percent crop treated adjustment factors, when used, ranged from 1%, for the national soybean crop acreage, to 25%, for the national watermelon acreage. The percent of the crop treated with benomyl calculations are based on CDFA, DPR and USDA multi-year data. Two dietary groupings were evaluated for chronic dietary exposures (Table 2). The non-PCT chronic exposures ranged from 0.000704 mg/kg/day, nursing infants, <1 year to 0.003223 mg/kg/day, children 1-6 years. The second, supplemental, chronic dietary was modified to include percent of the crop treated and commercial processing effects information. Chronic exposures modified with PCT adjustments ranged from 0.000321 mg/kg/day, females 13 + years (pregnant, not nursing) to 0.001263 mg/kg/day, non-nursing infants, <1 year. Two chronic dietary exposures were also calculated for both the Q1 and Q1* values. The Q1 cancer potency value for benomyl is 0.0043 (mg/kg/day)⁻¹. The unmodified chronic dietary risk value for the U.S. population (all) was 7.9E-06 and for the PCT modified chronic U.S. population (all) was 1.92E-06 (Table 2). The Q1* value for benomyl is 0.0067 (mg/kg/day)⁻¹ and the unmodified chronic dietary risk value for the U.S. population (all) was 1.23E-05 and for the PCT modified chronic U.S. population (all) was 3.0E-06.

An acute tolerance assessment at the U.S. EPA tolerances maximum residue contribution (MRC) level was performed on 20 individual RAC tolerances using the benomyl acute NOEL value of 15.0 mg/kg/day. There are over 80 current RAC or crop group tolerances for benomyl. The acute tolerance assessment margins of exposure (MOEs) were not greater than 100 for all of the RACs analyzed. There are 8 RACs that had at least one population subgroup with MOEs of less than 100: apple, grape, raisin, orange, peach, pear, pineapple and tomato (products). The MRC 95th percentile of exposure MOEs for the population subgroups ranged from 11 (exposure: 1.361169 mg/kg/day) for the nursing infants < 1 year/orange RAC combination to 212,382 (exposure: 0.000071 mg/kg/day) for Males 13 - 19 years/raspberry combination.

The only changes from the June, 1997 benomyl dietary exposure summary writeup are; updating the dietary exposure runs to reflect the new NOELs (15 mg/kg/day for both acute and chronic) and running a new acute tolerance commodity assessment. The residue values, food forms, percent of the crop treated or processing factors were not changed in this updated summary.

II. Introduction

Acute and chronic, including oncogenicity, dietary exposure assessments and an acute tolerance assessment were conducted for benomyl (40 CFR #180.294). All available benomyl raw agricultural commodity (RAC) residue data were evaluated (Table 1). The 40 CFR 180.294 tolerance is characterized as total benomyl parent material along with its toxicologically significant benzimidazole containing moieties (CFR, 1998).

All of the federal and state pesticide residue regulatory monitoring programs check for benomyl and/or its significant degradates. The detections are either as benomyl or as benomyl as determined from carbendazim (a degradation product). The Food and Drug Administration (FDA) monitoring program analyzes for the pesticide benomyl as carbendazim. The United States Department of Agriculture (USDA) Pesticide Data Program (PDP) also monitors for benomyl measured as carbendazim. The USDA Food Safety Inspection Service (FSIS) meat program measures for benomyl as does the California Department of Pesticide Regulation (DPR).

The FDA multiple residue screen limit of quantification (LOQ) level for benomyl parent material and metabolites, measured and reported as carbendazim, is 0.05 ppm (0.06 ppm for whole tomato). There were detected residues of benomyl, reported as carbendazim, found on many RACs during the Fiscal Year (FY) 1989-1994 surveillance period in the FDA monitoring programs (FDA, 1990-1995).

The USDA PDP program has monitored for benomyl since 1990 and there have been detections. Only the 1992 PDP data were used since the statistical reliability of the 1990 and 1991 data may be incomplete. All the 1992 PDP benomyl analyses were performed at the Gulfport, Mississippi APHIS laboratory. The benomyl and metabolites, reported as carbendazim, residue limit of detection (LOD) is 50 ppb and the limit of quantification (LOQ) is 100 ppb. Four (apple, banana, broccoli, and green beans) of the twelve RACs included in the 1992 PDP survey were checked for benomyl measured as carbendazim residues (USDA, 1994c). Broccoli had no detectable benomyl residues.

The USDA Food Safety Inspection Service (FSIS) meat monitoring program has checked for benomyl in poultry livers. There have been no detections reported on any of the sample analyses performed between 1988 - 1991. The total number of poultry livers, both chicken and turkey, analyzed were 896. The USDA FSIS meat monitoring program lowest detection level (LDL) is 0.05 ppm for benomyl in poultry liver tissues (USDA, 1990a,b, 1991b, 1994b).

The DPR benomyl parent material MDL has not been established and is not part of the routine multiple residue screen analysis program (CDFA, 1991). The consulted DPR programs were: a) priority pesticide program (program 1), b) preharvest program (program 3), and c) market basket surveillance (program 4). Benomyl is only analyzed for, as a single analyte residue, under the DPR priority pesticide program. Benomyl residues were detected in commodities analyzed under the DPR priority program during the 1989, 1990, 1991 and 1992 years (DPR, 1990-1993a).

E. I. du Pont de Nemours holds the registration for the only current California agricultural food use registration of the fungicide active ingredient benomyl. The E. I. du Pont Company benomyl product trade name used in all the submitted raw agricultural commodity (RAC) field residue studies is Benlate®. The common chemical name is benomyl, with the chemical name: methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate (CFR, 1998, du Pont, 1973). The potential residues on commodities from RACs treated with benomyl at various label rates, including the maximum, were evaluated by E. I. du Pont and reported in the submitted field studies. The registrant MDL for benomyl varied, depending on the age of the study and the specific RAC analyzed. The registrant analytical methods were either benomyl measured as total benomyl, in the older studies, or benomyl and metabolites reported as carbendazim (MBC). The MDL range varied, depending on commodity and study age, from 0.02 ppm to 0.1 ppm for all the submitted field studies that were cited (du Pont, 1968a-1990, Eickhoff *et al.*, 1989, Eickhoff and Petersen, 1990, Gabrielson, 1977, Haglund, 1978, Mulcahey *et al.*, 1993, Ogawa and Marmor, 1984, and Sumner, 1978).

There are currently two active registrations of benomyl approved for use in California. One registration is for agricultural use and the other for home and garden use. These two systemic foliar fungicide products are used for general fungus control. There is one du Pont product, Benlate SP™, and a Green Light benomyl product. The benomyl percent active ingredient is 50% for both of the California registered products. The Green Light registration is for home and garden use. The du Pont registration is the only product registered for agricultural uses and is also the only product with pre-harvest interval (PHI) requirement for crops. The PHI ranges from 0 days for seedling drenches and treated seeds to 80 days for nut crop applications. There was a total of 123,799 pounds of benomyl applied in California during the 1991 season (DPR, 1993b). There was a total of 151,974 pounds of benomyl applied in California during the 1994 season (DPR, 1996a). Also, during the 1995 season in California, there was a total of 197,050 pounds of benomyl applied (DPR, 1996b).

III. Residue Database

The majority of the RAC residue data used for the DPR benomyl dietary exposure analysis were obtained from the following sources: a) registrant commodity field residue studies or contracted analysis, b) FDA residue monitoring program data, c) DPR residue monitoring program data, or d) USDA 1992 PDP monitoring program data. A U.S. EPA tolerance value was used in the dietary exposure analysis for several RACs. This was done when residue or monitoring data were not available. All available benomyl raw agricultural commodity residue data are presented in Table 1.

Table 1. Summary of Benomyl Residues as of June, 1997.

RAC	Source ¹ (reference)	Tolerance ² (ppm)	Residue Used (ppm)		N ³	Additional Information
			Acute	Chronic		
Almond nut	Regsur (11, 23)	0.2 (Neg)	0.1	0.05	7	Macadamia nut as surrogate
Apple	FDA-GP (29...34)	7.0	1.70	0.04	2464	FDA & FDA Gulfport data
Apple - juice	FDA-GP (29...34)	7.0 (for RAC)	0.05	0.025	114	FDA & FDA Gulfport data
Apricot	FDA (29...34)	15.0	0.67	0.058	52	FDA surveillance data
Banana	PDP (52)	1.0	0.12	0.025	406	USDA 1992 PDP
Barley grain	Reg-f (21)	0.2	0.1	0.05	2	Registrant MDLs
Bean, Dry	Reg-f (23)	2.0	0.1	0.05	3	Registrant MDLs
Bean, Succulent	PDP (52)	2.0	0.89	0.04	142	USDA 1992 PDP residues
Beet, Sugar (root)	Reg-f (13)	0.2	0.1	0.05	12	Registrant MDLs
Blackberry	FDAsur (29...34)	7.0	0.56	0.23	6	Blueberry as surrogate data
Blueberry	FDA (20, 29...34)	7.0	0.56	0.23	6	FDA surveillance data
Boysenberry	FDAsur (29...34)	7.0	0.2	0.12	2	FDA surveillance data
Broccoli	PDP (52)	0.2	0.05	0.025	139	USDA 1992 PDP residues
Brussels Sprout	Reg-f (23)	15.0	5.17	3.77	3	Registrant residues
Cabbage, red & green	Regsur (22)	0.2	0.2	0.2	3	Tolerance: Registrant #s
Cantaloupe	DPR (4...7, 16)	1.0	0.05	0.025	4	DPR surveillance data
Carrot	Reg-f (37)	0.2	0.2	0.086	18	Registrant residues
Cattle, fat	RegTAS (26)	0.1	0.0007	0.0007	-	TAS extrapolated residues
Cattle, MBYP	RegTAS (26)	0.1	0.075	0.075	-	TAS extrapolated residues
Cattle, meat	RegTAS (26)	0.1	0.0004	0.0004	-	TAS extrapolated residues
Cauliflower	EPA (3)	0.2	0.2	0.2	-	U.S. EPA Tolerance
Celery	DPR (4...7)	3.0	0.49	0.06	30	DPR surveillance data
Cherry	FDA (29...34)	15.0	0.55	0.052	31	FDA surveillance data
Chinese Cabbage	Reg-f (22)	0.2	0.2	0.2	3	Tolerance: Registrant #s
Collard	Reg-f (35)	0.2	0.06	0.043	4	Registrant residues
Corn, fresh	FDA (29...34)	0.2	0.05	0.025	319	FDA surveillance MDLs
Cucumber	DPR (4...7, 16)	1.0	0.26	0.14	3	DPR surveillance data
Currant	FDAsur (29...34)	7.0	0.56	0.23	6	FDA surveillance data
Eggplant	Reg-f (23)	0.2	0.06	0.016	8	Registrant residues
Egg	RegTAS (26)	0.1	0.0002	0.0002	-	TAS extrapolated residues
Filbert nut	Regsur (23)	0.2 (Neg)	0.1	0.05	7	Macadamia nut as surrogate
Garlic	EPA (3)	0.2	0.2	0.2	-	U.S. EPA tolerance

Table 1. Summary of Benomyl Residues as of June, 1997 (continued).

RAC	Source ¹ (reference)	Tolerance ² (ppm)	Residue Used (ppm)		N ³	Additional Information
			Acute	Chronic		
Goat, fat	RegTAS (26)	0.1	0.0007	0.0007	-	TAS extrapolated beef resid.
Goat, MBYP	RegTAS (26)	0.1	0.075	0.075	-	TAS extrapolated beef resid.
Goat, meat	RegTAS (26)	0.1	0.0004	0.0004	-	TAS extrapolated beef resid.
Grape	DPR (4...7)	10.0	0.06	0.016	19	DPR surveillance data
Grape - juice	FDA (29...34)	10.0 (for RAC)	0.05	0.025	32	FDA surveillance data
Grapefruit	FDA (15, 29...34)	10.0	1.64	0.18	35	FDA surveillance data
Hog, fat	RegTAS (26)	0.1	0.0001	0.0001	-	TAS extrapolated beef resid.
Hog, MBYP	RegTAS (26)	0.1	0.013	0.013	-	TAS extrapolated beef resid.
Hog, meat	RegTAS (26)	0.1	0.0001	0.0001	-	TAS extrapolated beef resid.
Horse, fat	RegTAS (26)	0.1	0.0007	0.0007	-	TAS extrapolated beef resid.
Horse, MBYP	RegTAS (26)	0.1	0.075	0.075	-	TAS extrapolated beef resid.
Horse, meat	RegTAS (26)	0.1	0.0004	0.0004	-	TAS extrapolated beef resid.
Kale	EPA (3)	0.2	0.2	0.2	-	U.S. EPA tolerance
Kohlrabi	EPA (3)	0.2	0.2	0.2	-	U.S. EPA tolerance
Lemon	FDA (15, 29...34)	10.0	3.7	0.44	23	FDA surveillance data
Lime	FDA-GP (15, 29...34)	10.0	0.05	0.025	4	FDA & FDA Gulfport data
Loganberry	FDAsur (29...34)	7.0	0.56	0.23	6	Blueberry as surrogate data
Macadamia nut	Reg-f (23)	0.2 (Neg)	0.1	0.05	7	Registrant MDLs
Mango	FDA (29...34)	3.0	0.05	0.025	486	FDA surveillance data
Melon (musk)	Reg-f (16)	1.0	0.28	0.22	3	Cantaloupe, surrogate data
Milk (whole)	RegTAS (24)	0.1	0.0012	0.0012	-	TAS extrapolated residues
Mushroom	FDA (29...34)	10.0	0.49	0.04	94	FDA surveillance data
Mustard Greens	Reg-f (35)	0.2	0.014	0.009	4	Registrant residues
Nectarine	FDA (29...34)	15.0	0.36	0.058	43	FDA surveillance data
Oat grain	Reg-f (21)	0.2	0.05	0.025	3	Registrant MDLs
Orange	FDA-GP (15, 29...34)	10.0	0.05	0.025	862	FDA & FDA Gulfport data
Orange - juice	FDA-GP (15, 29...34)	10.0	0.05	0.025	13	FDA surveillance data
Peach	FDA (4...7, 29...34)	15.0	1.95	0.14	66	FDA surveillance data
Peanut	Reg-f (23)	0.2	0.1	0.05	3	Registrant MDLs
Pear	FDA-GP (29...34)	7.0	0.05	0.025	571	FDA & FDA Gulfport data
Pecan nut	Regsur (23, 24)	0.2 (Neg)	0.1	0.05	7	Macadamia nut as surrogate
Pepper (all)	Reg-f (23)	0.2	0.09	0.021	8	Registrant residues
Pineapple	FDA (29...34)	35.0	7.48	0.27	65	FDA surveillance data
Pistachio nut	Reg-f (38)	0.2 (Regional)	0.05	0.025	3	Registrant MDLs
Plum	FDA (29...34)	15.0	0.05	0.025	46	FDA surveillance data
Poultry, fat	RegTAS (26)	0.1	0.0021	0.0021	-	TAS extrapolated residues
Poultry, Liver	RegTAS (26,42,43,45,51)	0.2	0.0021	0.0021	-	TAS extrapolated residues
Poultry, MBYP	RegTAS (26)	0.1	0.0021	0.0021	-	TAS extrapolated residues
Poultry, meat	RegTAS (26)	0.1	0.00005	0.00005	-	TAS extrapolated residues
Pumpkin	Regsur (16)	1.0	0.55	0.5	3	Squash data as surrogate
Raisin	FDA-GP (29...34)	50.0 (as FA)	0.05	0.025	122	FDA & FDA Gulfport data
Raspberry	FDA (29...34)	7.0	0.2	0.12	2	FDA surveillance data
Rice	Reg-f (19, 24)	5.0	0.3	0.11	4	Registrant residues
Rutabaga - root	Regsur (25, 35)	0.2	0.034	0.022	4	Turnip root data surrogate
Rye grain	Regsur (21)	0.2	0.05	0.025	3	Oat grain data as surrogate
Sheep, fat	RegTAS (26)	0.1	0.0007	0.0007	-	TAS extrapolated beef resid.
Sheep, MBYP	RegTAS (26)	0.1	0.075	0.075	-	TAS extrapolated beef resid.
Sheep, meat	RegTAS (26)	0.1	0.0004	0.0004	-	TAS extrapolated beef resid.
Soybean	Reg-f (18)	0.2	0.05	0.025	13	Registrant MDLs
Spinach	Reg-f (36)	0.2	0.1	0.05	2	Registrant MDLs
Squash - summer	Reg-f (12, 16)	1.0	0.55	0.5	3	Registrant residues
Squash - winter	Regsur (16)	1.0	0.55	0.5	3	Sum. Squash as surrogate
Strawberry	DPR (4...7)	5.0	0.98	0.12	36	DPR surveillance data
Sweet Potato	DPR (4...7)	0.2	0.05	0.025	2	DPR surveillance data
Tangerine	FDA (15, 29...34)	10.0	1.64	0.18	35	FDA Grapefruit surrogate
Tomato	Reg-f (17, 23...26)	5.0	2.9	2.75	2	Registrant residues

(continued)

Table 1. Summary of Benomyl Residues as of June, 1997 (continued).

RAC	Source ¹ (reference)	Tolerance ² (ppm)	Residue Used (ppm)		N ³	Additional Information
			Acute	Chronic		
Tomato - juice	Reg-pr (17, 23...26)	5.0	0.4	0.4	2	Registrant processing resid.
Tomato - paste & puree	FDA-GP (17, 29...34)	50.0 (as FA)	0.05	0.025	73	FDA Gulfport residue data
Turnip - root	Reg-f (35, 39)	0.2	0.034	0.022	4	Turnip root residue data
Walnut	Regsur (23)	0.2 (Neg)	0.1	0.05	7	Macadamia nut as surrogate
Watermelon	Reg-f (16, 24)	1.0	0.14	0.13	3	Registrant residues
Wheat grain	Reg-fp (21)	0.2	0.05	0.025	2	Processed grain residues

- 1/ **DPR** = California Department of Pesticide Regulation pesticide monitoring program,
Reg-f = Registrant supplied field residue data, **Reg-fp** = Registrant supplied field residue data with processing component,
Reg-pr = Registrant supplied RAC processing study data,
RegTAS = Registrant sponsored dietary exposure analysis conducted by TAS, Inc., Washington, D.C.,
FDA = U.S. Food and Drug Administration pesticide monitoring program,
FDA-GP = FDA Gulfport lab 1990-91 special analysis of additional commodities frequently consumed by infants and children
FDAsur = FDA analyzed residue values used as surrogate for a similar RAC
PDP = U.S. Depart of Ag. Pesticide Data Program 1992 pesticide monitoring program, **U.S. EPA** = 40 CFR 180.422 tolerance value
2/ **FA** = Food Additive tolerance. Addressed through processing studies of specific RAC., **Neg** = U.S. EPA negligible residue tolerance.
3/ **N** = The number of RAC composite samples analyzed from the selected submitted studies or monitoring programs
Bold Type: Indicates that the RAC has a post harvest application tolerance. Pineapple has both pre and post harvest tolerances.

A. Primary RAC Residues (specific interest crops)

A comprehensive summary of the residue data for three specific primary RACs with U.S. EPA benomyl tolerances; orange, peach and tomato (both fresh market and processing) are discussed based on their contribution to the overall dietary exposure. These RACs, in addition to being presented in Table 1, are also explained in detail regarding the origin of their selected residue values used in the DPR dietary exposure analysis (TAS, 1996 a,b). These three RACs were chosen because of their contribution to the overall anticipated dietary exposure derived from a dietary exposure Critical Commodity Analysis (TAS, 1996a).

1. Orange (fresh and juice)

The U.S. EPA section 408 raw food tolerance for citrus fruits (including orange) is 10.0 ppm (CFR, 1998). The registrant has U.S. EPA tolerances for benomyl citrus fruits registrations for both pre-harvest and post-harvest applications. The current label allows for a maximum benomyl use rate of no more than 3.0 pounds (lbs) of active ingredient (a.i.) per acre per year for citrus (including orange) applied only as an orchard spray. There has been no post-harvest treatment allowed on the benomyl state and federal labels since 1991. The registrant analysis method for citrus measured total benomyl (including metabolites) and reported residues as carbendazim (MBC). There was 1 registrant study, which contained a summary of 5 submitted 1969 orange postharvest treatment studies, available to DPR (du Pont, 1974a). The analysis method MDL for benomyl residues is 0.05 ppm in the submitted postharvest studies (du Pont, 1974a). The summarized registrant studies were not used in the dietary analysis because the residue data were derived from only postharvest fruit dip or spray treatments and not from an orchard spray application which is the only label approved use. The registrant MDLs were the same as those available from the FDA monitoring programs which were used. The FDA monitoring data represent residue values that are derived closer to the consumer level.

The FDA FY 1989 - 1995 U.S. domestic monitoring programs tested 862 orange fruit and 13 orange juice commodity product samples. The RAC orange was selected for additional examination during 1990 and 1991 at the FDA Gulfport, Mississippi facility due to the increased evaluation of commodities that are frequently consumed by infants and children. There were no detected residues reported on raw oranges or orange juice during this period by the FDA (FDA, 1990-1995). The FDA

limit of quantification (LOQ) level for benomyl parent material and metabolites, measured and reported as carbendazim, is 0.05 ppm. The DPR 1989-1992 state program 1 monitoring did not select and test samples of oranges for benomyl residues. Because of the lack of detectable residues after extensive testing and the low LOQ used in the FDA monitoring program, the FDA Gulfport data and surveillance monitoring data were used to represent the raw orange and orange juice residues in the DPR dietary exposure analysis. The LOQ value of 0.05 ppm was used to represent residues for the acute analysis and 0.025 ppm (½ LOQ) value was used for the chronic dietary exposure analysis.

2. Peach

The U.S. EPA section 408 raw food tolerance for peach is 15.0 ppm (CFR, 1998). The RAC peach has U.S. EPA tolerances for both pre-harvest and post-harvest applications of benomyl. The current label registrations maximum benomyl use rate is for no more than 2.0 pounds (lbs) active ingredient (a.i.) per acre per growing season for peaches (stone fruit) applied as foliar spray (no post-harvest treatment). There were two registrant submitted peach summary field studies available to DPR (Eickhoff *et al.*, 1989, Eickhoff and Petersen, 1990). These two studies were not used in the dietary analysis because of the summary nature of the registrant data and the availability of both state and federal multi-year monitoring data.

The DPR 1989 - 1992 State pesticide monitoring Program 1 (Focused) tested 15 samples of peaches for benomyl residues. There were 3 detected residues (2.0, 1.25, and 0.2 ppm, 0.05 ppm MDL).

The FDA FY 1989 - 1995 U.S. domestic monitoring programs tested 66 peach commodity samples. The FDA limit of quantification (LOQ) level for benomyl parent material and metabolites, measured and reported as carbendazim, is 0.05 ppm for peach. There were 19 detected residues, range: 0.05 ppm (trace) - 1.951 ppm, 47 samples had no detectable residues and an overall sampling average of 0.14 ppm (FDA, 1990-1995). Because of the greater number of analyzed samples and the lower LOQ of the FDA monitoring program compared to the registrant data, the FDA surveillance monitoring data were used to represent the residues in the dietary exposure analysis. The value of 1.95 ppm was used to represent the residue for the acute analysis and the average sampling value of 0.14 ppm was used for the chronic dietary exposure analysis.

3. Tomato (whole fruit, juice and other products)

The U.S. EPA section 408 raw food tomato tolerance is 5.0 ppm (CFR, 1998). The current maximum Benomyl use rate is for no more than 2.5 pounds (lbs) of active ingredient (a.i.) per acre per year applied as a foliar spray to tomatoes (du Pont, 1975a). There is a 1 day preharvest interval for tomatoes sprayed with benomyl.

The DPR 1989 - 1992 domestic state monitoring programs did not test any whole tomato samples for Benomyl residues. No benomyl residues were tested for by DPR monitoring programs therefore, in the dietary exposure, analysis either registrant or FDA data were used to represent tomato residue values (DPR, 1990-1993a).

The whole tomato residue values were generated from data collected by registrant field studies (du Pont, 1975a). A total of 14 studies, conducted between 1968 and 1972, were contained in the submitted registrant data. The MDL value for all of the studies was 0.1 ppm. Twelve of the 14 registrant field studies used seasonal rates of 2.25 lbs a.i. per acre or less, which is below the label annual maximum of 2.5 lbs a.i. per acre. These 12 studies were not used since they were applied at less than the current label annual maximum rate. Only two 1972 studies, both from Chula Vista, California, of the 14 submitted contained maximum seasonal application rates of 2.5 lbs or more and also used a 1 day preharvest interval (du Pont, 1975a). The first study, with an application rate of 1.0 lb. a.i. per acre and a total of 3 applications (3.0 lbs a.i.), was 20% higher than the maximum label rate. The second satisfactory study also had an application rate of 1.0 lb. a.i. per acre but with a total of 4 applications (4.0 lbs a.i.). This rate was 60% higher than the maximum label allowed rate. The first study, 3.0 lbs a.i. total, had one composite sample with a residue level of 2.9 ppm. The second study,

at 4.0 lbs a.i. total benomyl per acre, had one composite sample but with a residue level of 2.6 ppm. The residue values used for whole tomatoes (fresh and dried) will be 2.9 ppm for the acute dietary exposure residues. The value of 2.75 ppm (the average of the two studies residues) will be used for chronic dietary exposure.

A 1986 tomato processing study conducted by the National Food Laboratory Inc. for du Pont, study AMR-471-86 #2, was used to derive the total benomyl residue values to represent tomato juice (du Pont, 1989). The study used 7 applications of benomyl at a treatment rate of 1.0 lb. a.i. per acre (7.0 lbs a.i. total) and with a zero day preharvest interval (PHI). The results were tomato juice obtained from tomato paste was 0.07 ppm. The results for fresh canned tomato juice was 0.40 ppm. The latter tomato juice number, 0.40 ppm, will be used to represent both the acute and chronic dietary exposure values in the DPR dietary assessment.

The FDA FY 1990 - 1991 U.S. domestic monitoring Gulfport, Mississippi detailed analysis program tested 48 tomato paste and 25 tomato puree processed commodity samples (FDA, 1990-1995). The FDA limit of quantification (LOQ) level for benomyl parent material and metabolites, measured and reported as carbendazim, is 0.05 ppm for the processed tomato product (0.06 ppm for whole tomato). There was one detected residue, 0.05 ppm (trace), and 47 tomato paste samples that had no detectable residues (FDA, 1990-1995). There were no detected residues from the 25 tomato puree samples tested at the LOQ of 0.05 ppm (FDA, 1990-1995). Because of the greater number of analyzed samples from the FDA Gulfport monitoring program compared to the registrant processing study, the FDA monitoring data will be used to represent the residues of tomato paste and puree in the dietary exposure analysis (du Pont, 1975a, FDA, 1990-1995). The FDA derived value of 0.05 ppm (LOQ) will be used to represent the tomato paste and puree residues for the acute analysis. The value of 0.025 ppm ($\frac{1}{2}$ LOQ) will be used to represent the anticipated chronic tomato paste and puree residues in the dietary exposure analysis.

B. Other Primary RAC Residues

A summary of the residue data for the other primary RACs with U.S. EPA benomyl tolerances almond - wheat grain are presented in Table 1. These RACs are not explained in detail in the DPR dietary summary due to one or more of the following factors: a. no detectable residues were found in the FDA, DPR, or USDA PDP monitoring programs, b. the RACs have low commodity consumption rates, c. the detected residues are consistently well below tolerance levels and make these RACs of lesser concern and therefore these residue values do not need the detailed explanation that the orange, peach and tomato residue data required. Several RACs were exceptions in that no registrant field trial or governmental regulatory monitoring data were available to DPR therefore, the U.S. EPA tolerances were used (CFR, 1998 and U.S. EPA, 1987).

C. Secondary RAC Residues

1. Milk, Eggs and Meats

A summary of the secondary RAC residue data: Beef, all tissues, eggs, goat, horse, milk, pork, poultry and sheep are presented in Table 1. The secondary RAC residue values used in the DPR dietary exposure analysis were taken from a registrant contracted 1990 study conducted by TAS, Inc. (Eickhoff and Petersen, 1990). The TAS, Inc. analysis calculated anticipated residues for an anticipated benomyl acute dietary exposure. These same numbers were also used by DPR to represent the chronic dietary exposure residue values for the same commodities. No additional information other than that provided in Table 1 is required. No adjustments were required to be made, based on the U.S. EPA subdivision O guidelines, to the sources of animal feed by the DPR because all necessary adjustments had already been factored in by the TAS, Inc. dietary exposure analysis (Eickhoff and Petersen, 1990 and U.S. EPA, 1982).

IV. Residue Adjustments

A. Percent of the Crop Treated

The current DPR chronic dietary exposure analysis default assumption is that 100% of any crop is treated with the pesticide under consideration. When quality data are available that indicate that less than 100% of a commodity is treated with a specific pesticide, then on an individual commodity by pesticide combination basis, exceptions to the default assumptions can be made.

The assumption that 100% of the crop is treated with and will contain averaged residues for up to 70 years is unrealistic. Using the existing percent crop treated data, it is reasonable to revise the 100% treated assumption downward using more realistic pesticide treatment rates and use patterns.

Only commodities that used the registrant field residue trial data in the chronic dietary exposure assessment were considered for percent crop treated adjustments. Any market basket monitoring data values, average of the residues, already reflect the effect of not all of the acreage being treated with the pesticide. Registrant residue data is amenable to being adjusted, if these data exist, because in every case all crops were treated, the maximum label application rate and the minimum pre-harvest interval were used to derive a residue value. This is not reflective of actual practices and is borne out by the lower residue levels encountered in various market basket surveys versus the registrant field studies.

The method of percent of the crop treated adjustment has been employed as a comparison to the standard chronic dietary exposure assessment using six commodities that have benomyl tolerances. Tomato (fresh and processing), soybean, rice, watermelon, and pecan have benomyl use history at the federal and state level. DPR Pesticide Use Reports and CDFA crop statistics together with USDA Ag Field Crops Summary annuals were used. Very conservative assumptions were made when setting the percentage of crop treated adjustment factors for the chronic dietary exposure section for this commodity. Multiple years of benomyl use and acreage harvested data were evaluated at the federal level.

1. Pecan

The total planted California pecan acreage for 1991 was 2,600 (CDFA, 1993). The California pecan acreage represents less than 2% of the total annual U.S. pecan production (USDA, 1992b). Benomyl was not applied to any California pecan acreage during 1991 (DPR, 1993b). The United States pecan acreage is produced primarily in two states; Georgia and Texas. According to the USDA Agricultural Marketing Service (AMS), 1991 production acreage was not available due to the fluctuation in the number of trees harvested (planted or native) (USDA, 1992b). Based on USDA Agriculture Marketing Statistics data, benomyl average use was 6% of the acreage based on the two state range of 6% (Georgia) - 9% (Texas) for 1991 (USDA, 1992b). Derived from this pecan use data, a 10% crop adjustment factor will be used for pecan in the chronic dietary residue file. The actual use data indicates that on average 94% of the national pecan crop is not treated.

2. Soybean

There was no commercial California acreage planted during 1990, 1991, or 1992 (CDFA, 1993). The United States soybean acreage is produced in 29 states and 100% of the soybean acreage and use data were reported in the USDA AMS document. Florida had the least soybean acreage amounting to 80,000 acres and Illinois had the most with 9,000,000 acres. The total planted acreage amounted to 58,000,000 during 1990 (USDA, 1991a). Based on USDA Agriculture Marketing Statistics data, benomyl use was less than 1% of the 1990 acreage in the 29 production states (USDA, 1991a). There were no benomyl use data contained in the 1991 - 1993 USDA field crop reports. The USDA reports indicated that insufficient benomyl use report information was available to indicate actual benomyl use. Since the 1990 data indicated less than 1% use and covered the entire national soybean production, the 1990 data will be used to modify the chronic dietary. Derived from this soybean use data, a 1% crop adjustment factor will be used in the chronic dietary residue file.

3. Rice

Harvested California rice totaled between 350,000 - 400,000 acres during the 1991 and 1992 seasons (CDFA, 1993). The California acreage represented approximately 13% of the total 1992 U.S. rice crop of 3,125,000 acres. The USDA surveyed rice crop data originated from two states, Arkansas and Louisiana. The 1990 rice production was 1,800,000 acres, the 1991 production was 1,860,000 acres and 2,000,000 acres during 1992 which represented 62%, 65%, and 64% respectively of the total U.S.A. production (USDA, 1991a, 1992a and 1993a). The combined Arkansas, California, and Louisiana rice crop equals approximately 75% of the U.S. total annual production. Benomyl was not applied to any California rice during the 1991, 1994 or 1995 seasons (DPR, 1993a, 1996a,b). Benomyl was used on about 15% of the Arkansas and Louisiana rice acreage in each of the 1990 (3% of 1990 acres), 1991 and 1992 seasons (USDA, 1991a, 1992a and 1993a). Based on the USDA and DPR data, a 20% crop adjustment factor to conservatively represent the average annual 15% treatment total will be used for rice in the chronic dietary residue file.

4. Tomatoes (fresh market and processed)

The California fresh market tomato acreage totaled 40,000 acres during 1991 and 37,000 acres during 1992 (CDFA, 1993, USDA, 1993b). The 1992 California acreage of 37,000 represented approximately 35% of the total 1992 U.S. fresh market tomato crop of 105,100 acres. The United States acreage is located mainly in eight states; California, Florida, Georgia, Michigan, New Jersey, New York, North Carolina, and Texas (USDA, 1993b). The USDA AMS fresh market tomato pesticide records indicate that benomyl was used on 9% of the 1992 national acreage. Benomyl was applied to less than 1,200 of the 40,000 acres of California fresh market tomatoes in 1991 and to less than 4,000 of the 37,000 acres grown during the 1992 season (USDA, 1993b). The California two-year average of 7% for acres of fresh market tomatoes treated with benomyl is very close to the 1992 U.S. national average. Based on the USDA and DPR data, a 10% crop adjustment factor to represent the average annual 9% national treatment total will be used in the chronic dietary residue file.

The United States processed tomato acreage is produced primarily from five states; California, Michigan, New Jersey, New York, and Texas (USDA, 1993b). The California processed tomato acreage totaled 312,000 acres during 1991 and 242,000 acres during 1992 (CDFA, 1993, USDA, 1993b). The California crop of 242,000 acres represented approximately 96% of the total 1992 U.S. processed tomato crop of 252,000 acres. Michigan had the next largest acreage with production, in 1992, from 6,200 acres. The USDA AMS 1992 processed tomato records indicate that 1% of the national acres were treated with benomyl (USDA, 1993b). Benomyl was applied to less than 150 acres of the 1991 and to 170 acres of the 1992 California processed tomato crops (USDA, 1993b). The California acreage represents 96% of the total 1992 U.S. processed tomato crop and both the DPR and USDA records indicate that 1% or less of the national crop received any benomyl treatments. Based on these data, the processed tomato food forms (tomato juice, paste, and puree food form codes) used in the chronic dietary residue files will be adjusted to reflect the 1% of crop actually treated.

5. Watermelon

The California watermelon acreage represents about 9% of the annual U.S. watermelon harvest with the total planted California acreage during 1992 of approximately 15,000 acres (USDA, 1993b). There was no specific use listed in the DPR annual report regarding benomyl application on California watermelons in 1991. If the use on melons (general) is counted, then 2,700 acres of melons were treated (DPR, 1993b). It is not known if any of this was watermelon acreage. The United States commercial watermelon acreage is produced primarily in six states; Arizona, California, Florida, Georgia, North Carolina and Texas. Production from the six states during 1992 was 178,000 acres (USDA, 1993b). Based on USDA Agriculture Marketing Statistics data, benomyl use averaged 25% of the 1992 acreage from the 6 major production states (USDA, 1993b). Derived from this watermelon use data, a 25% crop adjustment factor will be used for watermelon in the chronic dietary residue file.

B. Commercial Processing

1. Orange

There is a processing study available in the open literature that indicated benomyl residues were removed from oranges by the effects of processing (Elkins, 1989). The data indicated that washing and removing the orange peels resulted in a reduction of residues of 98% from unwashed and unpeeled whole oranges. These data are useful because it indicates that processed oranges (washed and peeled fruit and juice) would likely have lower residues than the selected anticipated residues. These processing effects were not included in the DPR dietary exposure analysis. Only residues derived from registrant field studies using the maximum label rates and minimum pre-harvest intervals are considered the appropriate situation to apply processing effect changes. Since the FDA monitoring data were used, the orange processing study results were not used in the DPR chronic dietary exposure scenario that included the reduction in residues from the effects of processing and percent of the crop treated adjustments.

2. Peach

There is an open literature processing study that indicates benomyl residues are removed from peaches due to the effects of processing (FAO, 1988). The data indicated that the commercial washing of peaches results in a reduction of residues of up to 73% from unwashed whole peaches. Additionally, data indicate that the commercial washing and peel removal by lye results in a reduction of residues by up to 93% compared to control peaches. Finally, the above commercial processing effects plus canning resulted in the potential reduction of residues by 99% when compared to control whole peaches. Since the FDA monitoring data were used, the peach processing study results were not used in the DPR chronic dietary exposure scenario that showed the potential reduction in anticipated residues due to the effects of processing and percent of the crop treated adjustments.

3. Rice

There same 1988 United Nations Food and Agriculture Organization (FAO) processing study data the contained the benomyl residue reduction in processed peaches also contained residue reduction in rice information (FAO, 1988). The data indicated that the commercial processing and cooking of unmilled rice results in a reduction of residues by up to 99% when compared to the unmilled and uncooked form. Since the rice residue values used in the DPR chronic dietary exposure analysis were derived from registrant supplied rough rice field data, the FAO rice processing study information can appropriately be used (E.I. du Pont, 1976a, FAO, 1988). The registrant rough rice residues were 0.11 ppm using the maximum label approved application rates and were used to show anticipated residues in the unmodified DPR chronic dietary exposure analysis. A 99% reduction in anticipated benomyl rice residues due to processing and cooking were factored into the dietary analysis by changing the second adjustment factor in the TAS dietary analysis program from 1.0 to 0.015 (TAS, 1996a). Therefore, the anticipated benomyl rice residues reduced due to the effects of commercial processing and cooking rice were included in the second DPR chronic dietary exposure analysis scenario.

4. Tomato

The same open literature processing study by E.R. Elkins that indicate benomyl residues were removed from tomatoes due to the effects of various processing methods (Elkins, 1989). The data indicate that washing and or processing whole tomatoes resulted in a reduction of residues of 82% when compared to the unwashed and unpeeled whole tomatoes. The data also indicate that processing whole tomatoes into juice reduces residues by 86%. In addition, the processing of whole tomatoes into catsup results in a reduction of residues of 98% from unwashed and unpeeled whole tomatoes. Because of a registrant tomato processing study using the maximum label rates and minimum pre-harvest interval was available, these adjustments were not applied in the DPR chronic

dietary exposure assessment. However, the registrant whole tomato RAC residue values if adjusted by the Elkins processing study reduction factors data would result in anticipated residues of a similar magnitude as those derived from the registrant processing study. These data are important because they indicate that available consumer processed tomato products (washed whole fruit, catsup and juice) would likely have lower residues than the selected anticipated residues used in the DPR chronic dietary exposure analysis.

V. Dietary Exposure (Summary)

A. Acute Dietary Exposure

The acute dietary exposure values resulting from the use of the benomyl no observed effect level (NOEL) of 15.0 mg/kg/day derived from a rabbit developmental study were examined and the results are presented in Table 2. The acute dietary exposures ranged from 0.010010 mg/kg/day, females 13 + years (pregnant, not nursing) (benomyl margin of exposure, MOE: 1,500) to 0.038567 mg/kg/day, nursing infants, less than 1 year (benomyl MOE: 390). The complete acute dietary exposure analysis print out that includes all current U.S. EPA label approved benomyl uses is found in Appendix A.

B. Seasonal Dietary Exposure for California Workers

Benomyl, because of its extensive year around utilization on California crops, does not present a clearly defined sub-chronic use season for workers applying the pesticide. The Worker Health and Safety branch therefore has not calculated a seasonal California worker occupational exposure. The Health Assessment Section (HAS) of the Medical Toxicology branch has also determined that no seasonal exposure by workers would result in a subchronic dietary exposure. Therefore, none was calculated.

C. Chronic Dietary Exposure

The chronic non-oncogenic dietary exposure values obtained by using a NOEL also of 15.0 mg/kg/day, except it was derived from a dog study, were examined (Table 2). There were two chronic exposure scenarios (Appendix B). The first consisted of dietary exposure data without the use of any percent of the crop treated or the effects of processing on the RAC adjustments. The second had the chronic dietary exposure data for several commodities modified with percent of the crop treated and processing adjustments based on registrant, CDFA, DPR, FAO (WHO) and USDA NASS data.

The chronic dietary exposures for unmodified label approved commodities contributions ranged from 0.000704 mg/kg/day, nursing infants (benomyl MOE: 21,300) to 0.003223 mg/kg/day, children 1-6 years (benomyl MOE: 4,660). The chronic exposures for commodities modified by the use of percent of the crop treated (PCT) and the effects of processing the RAC ranged from 0.000321 mg/kg/day, females 13 + years, pregnant, not nursing (benomyl MOE: 46,670) to 0.001263 mg/kg/day, non-nursing infants, less than 1 year (benomyl MOE: 11,870). The complete chronic dietary exposure analyses that included all current U.S. EPA label approved benomyl uses are found in Appendix B.

D. Lifetime (Oncogenic) Dietary Exposure

The chronic oncogenic dietary exposure values for the U.S. Population (all seasons), to represent potential worker exposure, are also presented in Table 2. The cancer risk from chronic dietary exposure to benomyl was determined and the Q1 (MLE: maximum likelihood estimate) cancer potency value of 0.0043 (mg/kg/day)⁻¹ and the Q1* (UB: upper bound) cancer potency value of 0.0067 (mg/kg/day)⁻¹ were used. The chronic dietary exposure risk, using the unmodified label approved

Table 2. Dietary Margins of Exposure ^a from Anticipated Benomyl Residues on Raw Agricultural Commodities.

Population Subgroups	Acute Exposure ^b 95th Percentile (Margins of Exposure)	Chronic Exposure ^b Annualized (PCT Modified) (Margins of Exposure)
US Pop. all seasons	920	33,540
Western Region	860	29,610
Pacific Region	850	29,590
Hispanics	910	37,750
Non-Hispanic Whites	950	33,240
Non-Hispanic Blacks	770	34,670
Non-Hispanic Other	630	26,790
All infants	400	14,490
Infants (nursing, < 1 year)	390	30,450
Infants (non-nursing, < 1 year)	430	11,870
Children (1-6 years)	450	16,400
Children (7-12 years)	650	24,770
Females (13-19 years) (not pregnant, not nursing)	1,020	44,870
Females (20+ years) (not pregnant, not nursing)	1,170	39,160
Females (13-50 years)	1,170	43,680
Females (13+ years) (pregnant, not nursing)	1,500	46,670
Females (13+ years) (nursing)	510	24,670
Males (13-19 years)	1,430	46,360
Males (20+ years)	1,300	43,060
Seniors (55+ years)	1,130	34,310

a/ MOEs based on all label approved commodities. Exposure levels have been rounded off to 3 significant figures and were based on the 1989-1992 Continuing Survey of Food Intakes of Individuals.

b/ The acute and chronic residue files used anticipated residue values for the commodities.

c/ MOE = NOEL ÷ Exposure. A MOE of at least 100 is generally considered to be protective of human health when the NOEL (non-oncogenic) is based on animal data. The acute NOEL value of 15.0 mg/kg/day was used (rabbit; developmental toxicity study). The chronic NOEL value, also 15.0 mg/kg/day, was used (dog; 1 year; hepatotoxicity). The number of user days (range: 67% to 100% person days) from the 1989-91 CSFII database were acceptable for all the subpopulations analyzed.

commodities was 7.9E-06 for the MLE and for the UB was 1.23E-05. The chronic dietary exposure risk, using data modified with PCT and commodity processing effects was 1.92E-06 for the MLE and 3.0E-06 for the UB using the U.S. population (all seasons).

VI. Acute Tolerance Assessment

An acute tolerance assessment was performed for benomyl using the current U.S. EPA tolerances (CFR, 1998). The benomyl acute NOEL of 15.0 mg/kg-body wt/day was used to calculate margins of exposure based on a rabbit developmental toxicity study (post implantation losses). There are currently more than 80 human consumption RACs that have benomyl tolerances (CFR, 1998). A total of 20 individual commodities were analyzed. The 20 human consumption RACs with use tolerances listed in the 1998 Code of Federal Regulations were included in the tolerance assessment.

Margins of exposure (MOE) of less than 100 for 1 or more population subgroups were found in 8 different commodities at tolerance when using the benomyl acute NOEL value of 15.0 mg/kg-body wt/day. The highest acute tolerance residue contribution exposure (lowest MOE) was 1.360476 mg/kg-bw (MOE; 11) which occurred in the nursing infants <1 year population subgroup from potential orange (including juice) consumption. The lowest exposure (highest MOE) was obtained from the raspberry tolerance assessment of the population subgroup male 13-19 years; with a value of 0.000071 mg/kg-bw (MOE; 212,380). Additionally, three commodities; apple, pineapple and tomato processed products (catsup, juice, paste, and puree), with 4 or more population subgroups with less than 100 margins of exposure are listed separately (Table 3) from the remaining 17 tolerance evaluation summaries.

Twelve commodities of the 20 plus background RACs analyzed had MOE values greater than 100 for each population subgroup while 8 commodities did not. The 12 commodities with MOE values greater than 100 for all population subgroups are; apricot, blueberry, Brussel's sprouts, celery, cherry, mushroom, nectarine, plum, raspberry, rice, strawberry and tomato. The RAC apricot tolerance MOE range is non-nursing infant; 284 (0.052799 mg/kg-bw) - female 13-19 years; 9,969 (0.001505 mg/kg-bw). The MOE range for the blueberry tolerance is Hispanics; 872 (0.017198 mg/kg-bw) - females 13+ years (pregnant, not nursing); 6,670 (0.002249 mg/kg-bw). The RAC Brussel's Sprouts tolerance MOE range is seniors 55+ years; 193 (0.077734 mg/kg-bw) - Hispanics; 1,280 (0.011715 mg/kg-bw). The MOE range for the celery tolerance is children 1-6 years; 2,705 (0.017198 mg/kg-bw) - females 13+ years (pregnant, not nursing); 6,670 (0.002249 mg/kg-bw). The RAC cherry tolerance MOE range is non-nursing infant; 308 (0.048648 mg/kg-bw) - female 13-19 years; 4,901 (0.003061 mg/kg-bw). The MOE range for the mushroom tolerance is children 1-6 years; 737 (0.020366 mg/kg-bw) - nursing infants; 2,871 (0.005225 mg/kg-bw). The MOE range for the nectarine tolerance is children 1-6 years; 1166 (0.128974 mg/kg-bw) - females 13+ years (nursing); 476 (0.031482 mg/kg-bw). The MOE range for the plum tolerance is children 7-12 years; 129 (0.116459 mg/kg-bw) - females 13 - 19 years; 608 (0.024681 mg/kg-bw). The RAC raspberry tolerance MOE range is seniors 55+ years; 552 (0.027155 mg/kg-bw) - females 13 - 19 years; 212,382 (0.000071 mg/kg-bw). The MOE range for the rice tolerance is non-nursing infants; 492 (0.030501 mg/kg-bw) - females 13+ years (pregnant, not nursing); 1,792 (0.008371 mg/kg-bw). The RAC strawberry tolerance MOE range is non-Hispanic other; 167 (0.089883 mg/kg-bw) - non-nursing infants; 19,189 (0.000782 mg/kg-bw). Finally, the MOE range for the tomato (fresh and processed forms) tolerance is children 1-6 years; 351 (0.042759 mg/kg-bw) - seniors 55+ years; 876 (0.017132 mg/kg-bw).

Additionally, five commodities analyzed had MOE values greater than 100 for all but three or fewer population subgroups. The 5 commodities with MOE values greater than 100 except for three or fewer population subgroups are; grape (2 population subgroups with MOEs of < 100), raisin (1), orange (3), peach (3) and pear (3 population subgroups). The RAC grape tolerance MOE range is nursing infant; 52 (0.288487 mg/kg-bw) to females 13+ years (pregnant, not nursing); 664 (0.003061 mg/kg-bw). The raisin tolerance MOE range is children 1-6 years; 97 (0.153985 mg/kg-bw) to females 13+ years (pregnant, not nursing); 921 (0.016293 mg/kg-bw). The orange tolerance MOE range is

nursing infant; 11 (1.360476 mg/kg-bw) to females 20+ years; 401 (0.037443 mg/kg-bw). The peach tolerance MOE range is all infants; 64 (0.233589 mg/kg-bw) to females 13+ years (pregnant, not nursing); 534 (0.028111 mg/kg-bw). The pear tolerance MOE range is nursing infant; 55 (0.274920 mg/kg-bw) to females 13+ years (pregnant, not nursing); 1,609 (0.009320 mg/kg-bw).

The RACs apple (4), pineapple (12) and tomato processed products (12) are the only commodities with benomyl tolerances that have 4 or more of their analyzed populations result in margins of exposure values of less than 100 (Table 3). Table 3 is a complete summary of the 3 commodities with benomyl tolerances that have MOEs of less than 100 for 4 or more of their population subgroups.

Table 3. High Consumption RACs With Margins of Exposure ^a of Less than 100 For Some Population Subgroups from Tolerance Levels of Benomyl.

Commodity: Population Subgroup	Acute 95 th Percentile Margins of Exposure ^b		
	Apple ^c	Pineapple	Tomato (Processed)
US Pop. all seasons	170	80	90
Western Region	200	100	90
Pacific Region	220	90	90
Hispanics	160	40	70
Non-Hispanic Whites	170	100	90
Non-Hispanic Blacks	160	60	120
Non-Hispanic Other	150	30	100
All Infants	50	40	40
Infants (nursing, < 1 year)	30 (0.540187)	20 (0.793437)	40 (0.402840)
Infants (non-nursing, < 1 year)	60	70	60
Children (1-6 years)	80	30	50
Children (7-12 years)	170	70	80
Females (13-19 years) (not pregnant, not nursing)	320	130	110
Females (20+ years) (not pregnant, not nursing)	470	100	110
Females (13-50 years)	380	90	110
Females (13+ years) (pregnant, not nursing)	270	230 (0.064808)	90
Females (13+ years) (nursing)	130	90	130 (0.116420)
Males (13-19 years)	380	200	105
Males (20+ years)	520	130	100
Seniors (55+ years)	540 (0.027973)	130	100

^a/ MOEs based on label approved commodities. Exposure levels have been rounded off to 2 significant figures and were based on the 1989-1992 Continuing Survey of Food Intakes of Individuals.

^b/ The residue files used tolerance level values for the commodities. The number of user days from the 1989-91 CSFII database are acceptable since background commodities were included.

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APPENDIX A
Acute Dietary Exposures

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL

Section 3 Registration

Residue file name: BENOMYLA

Analysis date: 08-03-1999

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: Analysis using CSFII consumption database.

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
1	N	BLACKBERRIES	0.560000	1.00	1.00	FDA sur
2	N	BOYSENBERRIES	0.560000	1.00	1.00	FDA sur
3	N	DEWBERRIES	no consumption in survey			
4	N	LOGANBERRIES	no consumption in survey			
5	N	RASPBERRIES	0.200000	1.00	1.00	FDA
7	N	BLUEBERRIES	0.560000	1.00	1.00	FDA
10	N	CURRENTS	0.560000	1.00	1.00	FDA sur
13	N	GRAPES	0.060000	1.00	1.00	DPR
14	N	GRAPES-RAISINS	0.050000	1.00	1.00	FDA
15	N	GRAPES-JUICE	0.050000	1.00	1.00	FDA
17	N	STRAWBERRIES	0.980000	1.00	1.00	DPR
20	K	CITRUS CITRON	no consumption in survey			
22	K	GRAPEFRUIT-PEELED FRUIT	1.640000	1.00	1.00	FDA
23	K	GRAPEFRUIT-JUICE	1.640000	2.10	1.00	FDA
24	K	KUMQUATS	no consumption in survey			
26	K	LEMONS-PEELED FRUIT	3.700000	1.00	1.00	FDA
27	K	LEMONS-PEEL	3.700000	1.00	1.00	FDA
28	K	LEMONS-JUICE	3.700000	2.00	1.00	FDA
30	K	LIMES-PEELED FRUIT	0.050000	1.00	1.00	FDA-GP
31	K	LIMES-PEEL	0.050000	1.00	1.00	FDA-GP
32	K	LIMES-JUICE	0.050000	2.00	1.00	FDA-GF
33	K	ORANGES-JUICE-CONCENTRATE	0.050000	1.00	1.00	FDA-GI
34	K	ORANGES-PEELED FRUIT	0.050000	1.00	1.00	FDA-GJ
35	K	ORANGES-PEEL	0.050000	1.00	1.00	FDA-GK
36	K	ORANGES-JUICE	0.050000	1.00	1.00	FDA-G
37	K	TANGELOS	no consumption in survey			
38	K	TANGERINES	1.640000	1.00	1.00	FDA su
39	K	TANGERINES-JUICE	1.640000	2.30	1.00	FDA su
40	R	ALMONDS	0.100000	1.00	1.00	REG su
44	R	FILBERTS (HAZELNUTS)	0.100000	1.00	1.00	REG su
46	R	MACADAMIA NUTS (BUSH NUTS)	0.100000	1.00	1.00	REG
47	R	PECANS	0.100000	1.00	1.00	REGs
48	R	WALNUTS	0.100000	1.00	1.00	REGs
50	A	PISTACHIO NUTS	0.050000	1.00	1.00	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. FCTRS #1	#2	SOURCE CODE	
52	L	APPLES	1.700000	1.00	1.00	FDA-GP	
53	L	APPLES-DRIED	1.700000	8.00	1.00	FDA-GP	
54	L	APPLES-JUICE/CIDER	0.050000	1.00	1.00	FDA-GP	
56	L	PEARS	0.050000	1.00	1.00	FDA-GP	
57	L	PEARS-DRIED	0.050000	6.25	1.00	FDA-GP	
59	M	APRICOTS	0.670000	1.00	1.00	FDA	
60	M	APRICOTS-DRIED	0.670000	6.00	1.00	FDA	
61	M	CHERRIES	0.550000	1.00	1.00	FDA	
62	M	CHERRIES-DRIED	no consumption in survey				
63	M	CHERRIES-JUICE	0.550000	1.50	1.00	FDA	
64	M	NECTARINES	0.360000	1.00	1.00	FDA	
65	M	PEACHES	1.950000	1.00	1.00	FDA	
66	M	PEACHES-DRIED	1.950000	7.00	1.00	FDA	
67	M	PLUMS (DAMSONS)	0.500000	1.00	1.00	FDA	
68	M	PLUMS-PRUNES (DRIED)	0.050000	1.00	1.00	FDA	
69	M	PLUMS/PRUNE-JUICE	0.050000	1.40	1.00	FDA	
72	A	BANANAS	0.120000	1.00	1.00	PDP	
73	A	BANANAS-DRIED	0.120000	3.90	1.00	PDP	
80	A	MANGOES	0.050000	1.00	1.00	FDA	
89	A	PINEAPPLES-PEELED FRUIT	7.480000	1.00	1.00	FDA	
90	A	PINEAPPLES-DRIED	7.480000	5.00	1.00	FDA	
91	A	PINEAPPLES-JUICE	7.480000	1.70	1.00	FDA	
141	J	CANTALOUPE-NECTAR	no consumption in survey				
142	J	CANTALOUPE-PULP (MUSKMELON)	0.050000	1.00	1.00	DPR	
143	J	CASABAS	0.280000	1.00	1.00	REGsur	
144	J	CRENSHAW	no consumption in survey				
145	J	HONEYDEW MELONS	0.280000	1.00	1.00	REGsur	
146	J	PERSIAN MELONS	no consumption in survey				
147	J	WATERMELON	0.140000	1.00	1.00	REG	
148	J	CUCUMBERS	0.260000	1.00	1.00	DPR	
149	J	PUMPKIN	0.550000	1.00	1.00	REGsur	
150	J	SQUASH-SUMMER	0.550000	1.00	1.00	REG	
151	J	SQUASH-WINTER	0.550000	1.00	1.00	REGsur	
154	I	EGGPLANT	0.060000	1.00	1.00	REG	
155	I	PEPPERS-SWEET (GARDEN)	0.090000	1.00	1.00	REG	
156	I	CHILI PEPPERS (JALAPENO)	0.090000	1.00	1.00	REG	
159	I	TOMATOES-WHOLE	2.900000	1.00	1.00	REG	
160	I	TOMATOES-JUICE	0.400000	1.00	1.00	REG	
161	I	TOMATOES-PUREE	0.050000	1.00	1.00	FDA-GP	
162	I	TOMATOES-PASTE	0.050000	1.00	1.00	FDA-GP	
163	I	TOMATOES-CATSUP	0.070000	1.00	1.00	REG	

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
166	E	CELERY	0.490000	1.00	1.00	DPR
168	F	BROCCOLI	0.050000	1.00	1.00	PDP
169	F	BRUSSELS SPROUTS	5.170000	1.00	1.00	REG
170	F	CABBAGE-GREEN AND RED	0.200000	1.00	1.00	REGsur
171	F	CAULIFLOWER	0.200000	1.00	1.00	EPA
172	F	COLLARDS	0.060000	1.00	1.00	REG
173	F	CABBAGE-CHINESE/CELERY/BOK CHO	0.200000	1.00	1.00	REG
174	F	KALE	0.200000	1.00	1.00	EPA
175	F	KOHLRABI	0.200000	1.00	1.00	EPA
183	F	MUSTARD GREENS	0.014000	1.00	1.00	REG
186	E	SPINACH	0.100000	1.00	1.00	REG
198	B	CARROTS	0.200000	1.00	1.00	REG
202	D	GARLIC	0.200000	1.00	1.00	EPA
214	B	RUTABAGAS-ROOTS	no consumption in survey			
218	B	SWEET POTATOES (INCLUDING YAMS	0.050000	1.00	1.00	DPR
219	B	TURNIPS-ROOTS	0.034000	1.00	1.00	REG
227	G	BEANS-DRY-GREAT NORTHERN	no consumption in survey			
228	G	BEANS-DRY-KIDNEY	0.100000	1.00	1.00	REG
229	G	BEANS-DRY-LIMA	0.100000	1.00	1.00	REG
230	G	BEANS-DRY-NAVY (PEA)	0.100000	1.00	1.00	REG
231	G	BEANS-DRY-OTHER	0.100000	1.00	1.00	REG
232	G	BEANS-DRY-PINTO	0.100000	1.00	1.00	REG
233	G	BEANS-SUCCULENT-LIMA	0.890000	1.00	1.00	PDPsur
234	G	BEANS-SUCCULENT-GREEN	0.890000	1.00	1.00	PDP
235	G	BEANS-SUCCULENT-OTHER	0.890000	1.00	1.00	PDP
236	G	BEANS-SUCCULENT-YELLOW/WAX	0.890000	1.00	1.00	PDPsur
238	O	CORN/SWEET	0.050000	1.00	1.00	FDA
239	A	PEANUTS-WHOLE	no consumption in survey			
249	G	BEANS-DRY-BROADBEANS	0.100000	1.00	1.00	REG
250	G	BEANS-SUCCULENT-BROADBEANS	no consumption in survey			
251	G	BEANS-DRY-PIGEON BEANS	no consumption in survey			
253	G	BEANS-UNSPECIFIED	0.100000	1.00	1.00	REG
256	G	BEANS-DRY-HYACINTH	no consumption in survey			
257	G	BEANS-SUCCULENT-HYACINTH	no consumption in survey			
258	G	BEANS-DRY-BLACKEYE PEAS/COWPEA	0.100000	1.00	1.00	REG
259	G	BEANS-DRY-GARBANZO/CHICK PEA	0.100000	1.00	1.00	REG
261	A	MUSHROOMS	0.490000	1.00	1.00	FDA
265	O	BARLEY	0.100000	1.00	1.00	REG
266	O	CORN/GRAIN-ENDOSPERM	0.050000	1.00	1.00	FDA
267	O	CORN/GRAIN-BRAN	0.050000	1.00	1.00	FDA
268	O	CORN SUGAR	0.050000	1.50	1.00	FDA

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE	
269	O	OATS	0.050000	1.00	1.00	REG	
270	O	RICE-ROUGH (BROWN)	0.300000	1.00	1.00	REG	
271	O	RICE-MILLED (WHITE)	0.300000	1.00	1.00	REG	
272	O	RYE-ROUGH	0.050000	1.00	1.00	REG	
273	O	RYE-GERM	no consumption in survey				
274	O	RYE-FLOUR	0.050000	1.00	1.00	REG	
276	O	WHEAT-ROUGH	0.200000	1.00	1.00	REG	
277	O	WHEAT-GERM	0.050000	1.00	1.00	REGpro	
278	O	WHEAT-BRAN	0.050000	1.00	1.00	REGpro	
279	O	WHEAT-FLOUR	0.050000	1.00	1.00	REGpro	
282	B	BEET SUGAR	0.100000	1.00	1.00	REG	
289	O	CORN GRAIN-OIL	0.050000	1.00	1.00	FDA	
293	A	PEANUTS-OIL	0.100000	1.00	1.00	REG	
297	G	SOYBEANS-OIL	0.050000	1.00	1.00	REG	
304	G	SOYBEANS-MATURE SEEDS DRY	0.050000	1.00	1.00	REG	
305	G	SOYBEANS-FLOUR (FULL FAT)	0.050000	1.00	1.00	REG	
306	G	SOYBEANS-FLOUR (LOW FAT)	0.050000	1.00	1.00	REG	
307	G	SOYBEANS-FLOUR (DEFATTED)	0.050000	1.00	1.00	REG	
315	A	GRAPES-WINE AND SHERRY	0.060000	1.00	1.00	DPR	
318	X	MILK-NONFAT SOLIDS	0.001200	1.00	1.00	REGTAS	
319	X	MILK-FAT SOLIDS	0.005800	1.00	1.00	REGTAS	
320	X	MILK SUGAR (LACTOSE)	0.002600	1.00	1.00	REGTAS	
321	U	BEEF-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS	
322	U	BEEF(ORGAN MEATS) -OTHER	0.075000	1.00	1.00	REGTAS	
323	U	BEEF-DRIED	0.000400	1.92	1.00	REGTAS	
324	U	BEEF(BONELESS) -FAT	0.000700	1.00	1.00	REGTAS	
325	U	BEEF(ORGAN MEATS) -KIDNEY	0.004500	1.00	1.00	REGTAS	
326	U	BEEF(ORGAN MEATS) -LIVER	0.075000	1.00	1.00	REGTAS	
327	U	BEEF(BONELESS) -LEAN (FAT/FREE)	0.000400	1.00	1.00	REGTAS	
328	U	GOAT-MEAT BYPRODUCTS	no consumption in survey				
329	U	GOAT(ORGAN MEATS) -OTHER	0.075000	1.00	1.00	REGTAS	
330	U	GOAT(BONELESS) -FAT	no consumption in survey				
331	U	GOAT(ORGAN MEATS) -KIDNEY	no consumption in survey				
332	U	GOAT(ORGAN MEATS) -LIVER	no consumption in survey				
333	U	GOAT(BONELESS) -LEAN (FAT/FREE)	no consumption in survey				
334	U	HORSE	no consumption in survey				
336	U	SHEEP-MEAT BYPRODUCTS	no consumption in survey				
337	U	SHEEP(ORGAN MEATS) -OTHER	no consumption in survey				
338	U	SHEEP(BONELESS) -FAT	0.000700	1.00	1.00	REGTAS	
339	U	SHEEP(ORGAN MEATS) -KIDNEY	no consumption in survey				
340	U	SHEEP(ORGAN MEATS) -LIVER	no consumption in survey				
341	U	SHEEP(BONELESS) -LEAN (FAT FREE)	0.000400	1.00	1.00	REGTAS	
342	U	PORK-MEAT BYPRODUCTS	0.013000	1.00	1.00	REGTAS	
343	U	PORK(ORGAN MEATS) -OTHER	no consumption in survey				

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
344	U	PORK (BONELESS) -FAT	0.001000	1.00	1.00	REGTAS
345	U	PORK (ORGAN MEATS) -KIDNEY	no consumption in survey			
346	U	PORK (ORGAN MEATS) -LIVER	0.013000	1.00	1.00	REGTAS
347	U	PORK (BONELESS) -LEAN (FAT FREE)	0.000100	1.00	1.00	REGTAS
356	V	TURKEY-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
357	V	TURKEY- (BONELESS) -FAT	0.002100	1.00	1.00	REGTAS
358	V	TURKEY- (BONELESS) LEAN/FAT FREE	0.000050	1.00	1.00	REGTAS
359	V	TURKEY-UNSPECIFIED	no consumption in survey			
360	V	POULTRY-OTHER-LEAN (FAT FREE)	0.000050	1.00	1.00	REGTAS
361	V	POULTRY-OTHER-GIBLETS (LIVER)	no consumption in survey			
362	V	POULTRY-OTHER-FAT	0.002100	1.00	1.00	REGTAS
363	X	EGGS-WHOLE	0.000200	1.00	1.00	REGTAS
364	X	EGGS-WHITE ONLY	0.000200	1.00	1.00	REGTAS
365	X	EGGS-YOLK ONLY	0.000200	1.00	1.00	REGTAS
366	V	CHICKEN-BYPRODUCTS	no consumption in survey			
367	V	CHICKEN-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
368	V	CHICKEN (BONELESS) -FAT	0.002100	1.00	1.00	REGTAS
369	V	CHICKEN (BONELESS) LEAN/FAT FREE	0.000050	1.00	1.00	REGTAS
377	L	APPLES-JUICE-CONCENTRATE	0.050000	1.00	1.00	FDA-GP
378	A	BANANAS-NECTAR	0.120000	1.00	1.00	PDP
379	B	BEET SUGAR-MOLASSES	no consumption in survey			
380	N	BLACKBERRIES-JUICE	0.560000	1.00	1.00	FDAsur
383	F	CABBAGE-SAVOY	no consumption in survey			
384	E	CELERY JUICE	0.490000	1.00	1.00	DPR
385	V	CHICKEN-GIBLETS (EXCL. LIVER)	0.002100	1.00	1.00	REGTAS
388	O	CORN SUGAR-MOLASSES	0.050000	1.50	1.00	FDA
392	N	GRAPES-JUICE-CONCENTRATE	0.050000	1.00	1.00	FDA-GP
398	X	MILK-BASED WATER	0.001200	1.00	1.00	REGTAS
399	O	OATS-BRAN	0.050000	1.00	1.00	REG
402	M	PEACHES-JUICE	1.950000	1.00	1.00	FDA
403	A	PEANUT-BUTTER	0.100000	1.89	1.00	REG
404	L	PEARS-NECTAR	0.050000	1.00	1.00	FDA-GP
406	A	PINEAPPLES-JUICE-CONCENTRATE	7.480000	1.00	1.00	FDA
408	O	RICE-BRAN	0.300000	1.00	1.00	REG
409	O	RICE-WILD	0.300000	1.00	1.00	REG
410	M	APRICOT JUICE OR NECTAR	0.670000	1.00	1.00	FDA
416	N	STRAWBERRIES-JUICE	0.980000	1.00	1.00	DPR
420	K	TANGERINES-JUICE-CONCENTRATE	no consumption in survey			
423	I	TOMATOES-DRIED	2.900000	14.30	1.00	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
424	U	VEAL-(BONELESS)-FAT	0.000700	1.00	1.00	REGTAS
425	U	VEAL-(BONELESS)-LEAN (FAT FREE	0.000400	1.00	1.00	REGTAS
426	U	VEAL-(ORGAN MEATS)-KIDNEY	no consumption in survey			
427	U	VEAL-(ORGAN MEATS)-LIVER	no consumption in survey			
428	U	VEAL-(ORGAN MEATS)-OTHER	no consumption in survey			
429	U	VEAL-DRIED	no consumption in survey			
430	U	VEAL-MEAT BYPRODUCTS	no consumption in survey			
436	J	WATERMELON-JUICE	no consumption in survey			
437	O	WHEAT-GERM OIL	no consumption in survey			
441	K	GRAPEFRUIT-JUICE-CONCENTRATE	1.640000	8.26	1.00	FDA
442	K	LEMONS-JUICE-CONCENTRATE	3.700000	11.40	1.00	FDA
443	K	LIMES-JUICE-CONCENTRATE	0.050000	6.00	1.00	FDA
448	K	GRAPEFRUIT PEEL	no consumption in survey			
449	V	TURKEY-(ORGAN MEATS)-OTHER	0.002100	1.00	1.00	REGTAS
940	A	PEANUTS HULLED	0.100000	1.00	1.00	REG

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL

Section 3 Registration

Residue file name: BENOMYLA

Analysis date: 08-03-1999

1989-92 DATA Adjustment factor #2 NOT used

DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Initial estimate of user-days as % of person-days in survey = 100.00%

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: Analysis using CSFII consumption database.

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U.S. POP - ALL SEASONS

Daily Exposure Analysis 1/
(mg/kg body-weight/day)
per Capita per User

	per Capita	per User
Mean	0.004685	0.004697
Standard Deviation	0.009958	0.009967
Standard Error	0.000053	0.000053

Percent of Person-Days that are User-Days = 99.75%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000242	61,932	90.00	0.010909	1,375
20.00	0.000475	31,580	95.00	0.016347	918
30.00	0.000853	17,586	97.50	0.024180	620
40.00	0.001385	10,833	99.00	0.037685	398
50.00	0.002086	7,192	99.50	0.055831	269
60.00	0.003029	4,952	99.75	0.077581	193
70.00	0.004413	3,399	99.90	0.124952	120
80.00	0.006596	2,274			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000237	63,349	90.00	0.010898	1,376
20.00	0.000470	31,891	95.00	0.016334	918
30.00	0.000846	17,722	97.50	0.024160	621
40.00	0.001377	10,896	99.00	0.037663	398
50.00	0.002077	7,222	99.50	0.055786	269
60.00	0.003020	4,968	99.75	0.077527	193
70.00	0.004402	3,407	99.90	0.124874	120
80.00	0.006585	2,278			

1/ Analysis based on all participant-days in NFCS 1989-92 survey.

2/ Margin of Exposure = NOEL/ Dietary Exposure.

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

WESTERN REGION

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

	per Capita	per User
Mean	0.005272	0.005287
Standard Deviation	0.012470	0.012486
Standard Error	0.000143	0.000144

Percent of Person-Days that are User-Days = 99.71%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000263	57,056	90.00	0.012140	1,236
20.00	0.000541	27,743	95.00	0.017431	861
30.00	0.000998	15,034	97.50	0.026164	573
40.00	0.001550	9,675	99.00	0.041319	363
50.00	0.002332	6,432	99.50	0.069247	217
60.00	0.003354	4,472	99.75	0.096187	156
70.00	0.004882	3,072	99.90	0.178302	84
80.00	0.007143	2,100			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000256	58,610	90.00	0.012125	1,237
20.00	0.000534	28,083	95.00	0.017416	861
30.00	0.000988	15,178	97.50	0.026138	574
40.00	0.001541	9,737	99.00	0.041289	363
50.00	0.002320	6,464	99.50	0.069164	217
60.00	0.003342	4,488	99.75	0.096107	156
70.00	0.004869	3,081	99.90	0.178140	84
80.00	0.007130	2,104			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

HISPANICS

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.004878	0.004900
Standard Deviation	0.012074	0.012097
Standard Error	0.000208	0.000209

Percent of Person-Days that are User-Days = 99.55%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000206	72,731	90.00	0.011096	1,352
20.00	0.000437	34,324	95.00	0.016562	906
30.00	0.000719	20,862	97.50	0.022871	656
40.00	0.001139	13,164	99.00	0.039129	383
50.00	0.001827	8,211	99.50	0.096808	155
60.00	0.002822	5,316	99.75	0.124850	120
70.00	0.004294	3,493	99.90	0.155812	96
80.00	0.006412	2,339			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000198	75,833	90.00	0.011075	1,354
20.00	0.000429	34,996	95.00	0.016537	907
30.00	0.000710	21,126	97.50	0.022843	657
40.00	0.001128	13,298	99.00	0.039080	384
50.00	0.001811	8,282	99.50	0.096546	155
60.00	0.002803	5,351	99.75	0.124722	120
70.00	0.004274	3,509	99.90	0.155718	96
80.00	0.006393	2,346			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

NON-HISPANIC WHITES

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.004620	0.004631
Standard Deviation	0.009152	0.009159
Standard Error	0.000056	0.000056

Percent of Person-Days that are User-Days = 99.78%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000261	57,482	90.00	0.010859	1,381
20.00	0.000502	29,851	95.00	0.015736	953
30.00	0.000926	16,193	97.50	0.022891	655
40.00	0.001485	10,104	99.00	0.034653	433
50.00	0.002208	6,792	99.50	0.049038	306
60.00	0.003169	4,733	99.75	0.070259	213
70.00	0.004562	3,288	99.90	0.101775	147
80.00	0.006660	2,252			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000256	58,668	90.00	0.010849	1,383
20.00	0.000498	30,111	95.00	0.015725	954
30.00	0.000920	16,310	97.50	0.022874	656
40.00	0.001477	10,156	99.00	0.034635	433
50.00	0.002200	6,817	99.50	0.049006	306
60.00	0.003161	4,746	99.75	0.070212	214
70.00	0.004552	3,295	99.90	0.101728	147
80.00	0.006651	2,255			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

NON-HISPANIC BLACKS

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

	per Capita	per User
Mean	0.004557	0.004563
Standard Deviation	0.011003	0.011008
Standard Error	0.000158	0.000159

Percent of Person-Days that are User-Days = 99.88%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000164	91,538	90.00	0.010337	1,451
20.00	0.000338	44,375	95.00	0.019422	772
30.00	0.000588	25,514	97.50	0.031123	482
40.00	0.000952	15,757	99.00	0.046110	325
50.00	0.001492	10,052	99.50	0.059870	251
60.00	0.002221	6,753	99.75	0.089275	168
70.00	0.003201	4,686	99.90	0.126562	119
80.00	0.005322	2,819			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000162	92,547	90.00	0.010331	1,452
20.00	0.000336	44,597	95.00	0.019411	773
30.00	0.000586	25,607	97.50	0.031109	482
40.00	0.000949	15,801	99.00	0.046098	325
50.00	0.001489	10,074	99.50	0.059853	251
60.00	0.002218	6,764	99.75	0.089239	168
70.00	0.003198	4,691	99.90	0.126532	119
80.00	0.005317	2,821			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

NON-HISPANIC OTHER

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.006639	0.006699
Standard Deviation	0.017459	0.017527
Standard Error	0.000529	0.000533

Percent of Person-Days that are User-Days = 99.10%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000253	59,312	90.00	0.013485	1,112
20.00	0.000517	29,015	95.00	0.023672	634
30.00	0.001061	14,134	97.50	0.034560	434
40.00	0.001753	8,559	99.00	0.071134	211
50.00	0.002607	5,755	99.50	0.146658	102
60.00	0.003745	4,005	99.75	0.173789	86
70.00	0.005354	2,802	99.90	0.190068	79
80.00	0.007997	1,876			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000232	64,565	90.00	0.013435	1,116
20.00	0.000498	30,128	95.00	0.023580	636
30.00	0.001027	14,608	97.50	0.034462	435
40.00	0.001715	8,746	99.00	0.070914	212
50.00	0.002568	5,841	99.50	0.145975	103
60.00	0.003704	4,050	99.75	0.173544	86
70.00	0.005310	2,825	99.90	0.189970	79
80.00	0.007949	1,887			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

NURSING INFANTS (<1 YEAR)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

	per Capita	per User
Mean	0.007791	0.011554
Standard Deviation	0.038818	0.046813
Standard Error	0.003138	0.005019

Percent of Person-Days that are User-Days = 67.43%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000124	120,692	90.00	0.028120	533
20.00	0.000144	104,004	95.00	0.038567	389
30.00	0.000154	97,643	97.50	0.046380	323
40.00	0.000179	83,613	99.00	0.241604	62
50.00	0.000441	34,006	99.50	0.319846	47
60.00	0.000897	16,729	99.75	0.358967	42
70.00	0.001656	9,058	99.90	0.382439	39
80.00	0.006178	2,428			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE

in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000000	>1,000,000	90.00	0.017522	856
20.00	0.000000	>1,000,000	95.00	0.033521	447
30.00	0.000000	>1,000,000	97.50	0.042606	352
40.00	0.000126	118,751	99.00	0.178739	84
50.00	0.000150	100,186	99.50	0.282053	53
60.00	0.000197	76,075	99.75	0.340071	44
70.00	0.000692	21,674	99.90	0.374881	40
80.00	0.001810	8,289			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

NON-NURSING INFANTS (<1)

Daily Exposure Analysis
 (mg/kg body-weight/day)

	per Capita	per User
Mean	0.009242	0.009242
Standard Deviation	0.012637	0.012637
Standard Error	0.000594	0.000594

Percent of Person-Days that are User-Days =100.00%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000200	75,041	90.00	0.027749	541
20.00	0.000410	36,614	95.00	0.035290	425
30.00	0.001180	12,708	97.50	0.045107	333
40.00	0.002746	5,462	99.00	0.057709	260
50.00	0.004481	3,347	99.50	0.064164	234
60.00	0.006488	2,312	99.75	0.072432	207
70.00	0.009291	1,615	99.90	0.085853	175
80.00	0.014939	1,004			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000200	75,041	90.00	0.027749	541
20.00	0.000410	36,614	95.00	0.035290	425
30.00	0.001180	12,708	97.50	0.045107	333
40.00	0.002746	5,462	99.00	0.057709	260
50.00	0.004481	3,347	99.50	0.064164	234
60.00	0.006488	2,312	99.75	0.072432	207
70.00	0.009291	1,615	99.90	0.085853	175
80.00	0.014939	1,004			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

FEMALES (13+/PREG/NOT NSG)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.003367	0.003367
Standard Deviation	0.004951	0.004951
Standard Error	0.000251	0.000251

Percent of Person-Days that are User-Days =100.00%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000224	66,904	90.00	0.008049	1,864
20.00	0.000365	41,095	95.00	0.010010	1,498
30.00	0.000630	23,818	97.50	0.014414	1,041
40.00	0.000907	16,533	99.00	0.018625	805
50.00	0.001804	8,316	99.50	0.020722	724
60.00	0.002773	5,409	99.75	0.027130	553
70.00	0.004358	3,442	99.90	0.052981	283
80.00	0.005966	2,514			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000224	66,904	90.00	0.008049	1,864
20.00	0.000365	41,095	95.00	0.010010	1,498
30.00	0.000630	23,818	97.50	0.014414	1,041
40.00	0.000907	16,533	99.00	0.018625	805
50.00	0.001804	8,316	99.50	0.020722	724
60.00	0.002773	5,409	99.75	0.027130	553
70.00	0.004358	3,442	99.90	0.052981	283
80.00	0.005966	2,514			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

FEMALES (13+/NURSING)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

	per Capita	per User
Mean	0.007468	0.007468
Standard Deviation	0.012659	0.012659
Standard Error	0.000874	0.000874

Percent of Person-Days that are User-Days =100.00%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000344	43,635	90.00	0.022807	658
20.00	0.000550	27,268	95.00	0.029685	505
30.00	0.001040	14,417	97.50	0.037516	400
40.00	0.001532	9,789	99.00	0.052432	286
50.00	0.002189	6,853	99.50	0.077678	193
60.00	0.004678	3,207	99.75	0.094902	158
70.00	0.006685	2,244	99.90	0.106034	141
80.00	0.011192	1,340			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000344	43,635	90.00	0.022807	658
20.00	0.000550	27,268	95.00	0.029685	505
30.00	0.001040	14,417	97.50	0.037516	400
40.00	0.001532	9,789	99.00	0.052432	286
50.00	0.002189	6,853	99.50	0.077678	193
60.00	0.004678	3,207	99.75	0.094902	158
70.00	0.006685	2,244	99.90	0.106034	141
80.00	0.011192	1,340			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

CHILDREN (1-6 YEARS)

Daily Exposure Analysis
 (mg/kg body-weight/day)

	per Capita	per User
Mean	0.010299	0.010302
Standard Deviation	0.021372	0.021375
Standard Error	0.000346	0.000346

Percent of Person-Days that are User-Days = 99.97%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000653	22,959	90.00	0.022936	654
20.00	0.001115	13,458	95.00	0.033255	451
30.00	0.001747	8,588	97.50	0.045349	331
40.00	0.002715	5,525	99.00	0.105534	142
50.00	0.004095	3,663	99.50	0.159862	94
60.00	0.006637	2,260	99.75	0.212181	71
70.00	0.010272	1,460	99.90	0.246525	61
80.00	0.015013	999			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000652	23,021	90.00	0.022934	654
20.00	0.001113	13,472	95.00	0.033252	451
30.00	0.001745	8,594	97.50	0.045345	331
40.00	0.002713	5,529	99.00	0.105522	142
50.00	0.004093	3,665	99.50	0.159846	94
60.00	0.006634	2,261	99.75	0.212165	71
70.00	0.010269	1,461	99.90	0.246518	61
80.00	0.015010	999			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

CHILDREN (7-12 YEARS)

Daily Exposure Analysis
 (mg/kg body-weight/day)

	per Capita	per User
Mean	0.006816	0.006818
Standard Deviation	0.010119	0.010120
Standard Error	0.000173	0.000173

Percent of Person-Days that are User-Days = 99.98%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000469	31,993	90.00	0.016547	907
20.00	0.000833	18,000	95.00	0.023171	647
30.00	0.001412	10,626	97.50	0.030290	495
40.00	0.002229	6,731	99.00	0.047211	318
50.00	0.003394	4,420	99.50	0.058011	259
60.00	0.005308	2,826	99.75	0.076895	195
70.00	0.007524	1,994	99.90	0.123873	121
80.00	0.010724	1,399			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000468	32,064	90.00	0.016545	907
20.00	0.000833	18,016	95.00	0.023170	647
30.00	0.001411	10,633	97.50	0.030288	495
40.00	0.002227	6,735	99.00	0.047208	318
50.00	0.003392	4,422	99.50	0.058008	259
60.00	0.005306	2,827	99.75	0.076890	195
70.00	0.007522	1,994	99.90	0.123865	121
80.00	0.010722	1,399			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

MALES (13-19 YEARS)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.003073	0.003073
Standard Deviation	0.004065	0.004065
Standard Error	0.000104	0.000104

Percent of Person-Days that are User-Days =100.00%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000241	62,351	90.00	0.008064	1,860
20.00	0.000380	39,473	95.00	0.010507	1,428
30.00	0.000657	22,845	97.50	0.014373	1,044
40.00	0.001088	13,792	99.00	0.019246	779
50.00	0.001599	9,379	99.50	0.021305	704
60.00	0.002365	6,342	99.75	0.025803	581
70.00	0.003288	4,562	99.90	0.035793	419
80.00	0.004945	3,033			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000241	62,351	90.00	0.008064	1,860
20.00	0.000380	39,473	95.00	0.010507	1,428
30.00	0.000657	22,845	97.50	0.014373	1,044
40.00	0.001088	13,792	99.00	0.019246	779
50.00	0.001599	9,379	99.50	0.021305	704
60.00	0.002365	6,342	99.75	0.025803	581
70.00	0.003288	4,562	99.90	0.035793	419
80.00	0.004945	3,033			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

FEMALES (13-19 YRS/NP/NN)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.003838	0.003845
Standard Deviation	0.006591	0.006595
Standard Error	0.000158	0.000159

Percent of Person-Days that are User-Days = 99.81%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000212	70,829	90.00	0.009565	1,568
20.00	0.000374	40,108	95.00	0.014720	1,019
30.00	0.000584	25,678	97.50	0.022254	674
40.00	0.001027	14,602	99.00	0.036206	414
50.00	0.001577	9,510	99.50	0.042877	350
60.00	0.002357	6,365	99.75	0.047237	318
70.00	0.003430	4,373	99.90	0.056487	266
80.00	0.005498	2,728			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000208	72,046	90.00	0.009558	1,569
20.00	0.000372	40,371	95.00	0.014711	1,020
30.00	0.000581	25,800	97.50	0.022240	674
40.00	0.001022	14,673	99.00	0.036189	414
50.00	0.001572	9,541	99.50	0.042865	350
60.00	0.002351	6,381	99.75	0.047229	318
70.00	0.003424	4,381	99.90	0.056476	266
80.00	0.005490	2,732			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

MALES (20+ YEARS)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.003493	0.003496
Standard Deviation	0.005987	0.005988
Standard Error	0.000059	0.000059

Percent of Person-Days that are User-Days = 99.93%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000219	68,601	90.00	0.008275	1,813
20.00	0.000417	36,011	95.00	0.011528	1,301
30.00	0.000725	20,679	97.50	0.015577	963
40.00	0.001205	12,443	99.00	0.023863	629
50.00	0.001786	8,399	99.50	0.035268	425
60.00	0.002557	5,865	99.75	0.061203	245
70.00	0.003624	4,139	99.90	0.084014	179
80.00	0.005145	2,916			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000217	69,055	90.00	0.008273	1,813
20.00	0.000415	36,111	95.00	0.011526	1,301
30.00	0.000724	20,725	97.50	0.015574	963
40.00	0.001203	12,465	99.00	0.023859	629
50.00	0.001784	8,409	99.50	0.035260	425
60.00	0.002555	5,870	99.75	0.061184	245
70.00	0.003622	4,142	99.90	0.084003	179
80.00	0.005142	2,917			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

FEMALES (20+ YEARS/NP/NN)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

	per Capita	per User
Mean	0.003883	0.003890
Standard Deviation	0.006921	0.006925
Standard Error	0.000059	0.000059

Percent of Person-Days that are User-Days = 99.81%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000200	74,941	90.00	0.008900	1,685
20.00	0.000408	36,742	95.00	0.012870	1,165
30.00	0.000752	19,941	97.50	0.017806	842
40.00	0.001288	11,650	99.00	0.029733	504
50.00	0.001973	7,604	99.50	0.044013	341
60.00	0.002791	5,374	99.75	0.060991	246
70.00	0.004085	3,672	99.90	0.082790	181
80.00	0.005761	2,603			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000197	76,254	90.00	0.008894	1,686
20.00	0.000405	37,031	95.00	0.012863	1,166
30.00	0.000748	20,064	97.50	0.017796	843
40.00	0.001281	11,706	99.00	0.029718	505
50.00	0.001966	7,629	99.50	0.043986	341
60.00	0.002785	5,386	99.75	0.060959	246
70.00	0.004078	3,678	99.90	0.082763	181
80.00	0.005755	2,606			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

SENIORS (55+)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.004245	0.004251
Standard Deviation	0.007165	0.007169
Standard Error	0.000078	0.000078

Percent of Person-Days that are User-Days = 99.85%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000255	58,752	90.00	0.009410	1,594
20.00	0.000528	28,420	95.00	0.013242	1,133
30.00	0.000965	15,552	97.50	0.018242	822
40.00	0.001576	9,520	99.00	0.029568	507
50.00	0.002394	6,267	99.50	0.045779	328
60.00	0.003349	4,479	99.75	0.065104	230
70.00	0.004570	3,282	99.90	0.084013	179
80.00	0.006350	2,362			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000252	59,562	90.00	0.009405	1,595
20.00	0.000525	28,598	95.00	0.013237	1,133
30.00	0.000960	15,626	97.50	0.018234	823
40.00	0.001570	9,553	99.00	0.029556	508
50.00	0.002387	6,283	99.50	0.045755	328
60.00	0.003343	4,487	99.75	0.065074	231
70.00	0.004564	3,286	99.90	0.083994	179
80.00	0.006345	2,364			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

PACIFIC REGION

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

	per Capita	per User
Mean	0.005365	0.005377
Standard Deviation	0.013085	0.013096
Standard Error	0.000187	0.000187

Percent of Person-Days that are User-Days = 99.79%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000277	54,064	90.00	0.012329	1,217
20.00	0.000570	26,306	95.00	0.017711	847
30.00	0.001054	14,227	97.50	0.026258	571
40.00	0.001625	9,233	99.00	0.038811	386
50.00	0.002457	6,105	99.50	0.049170	305
60.00	0.003539	4,239	99.75	0.092791	162
70.00	0.005138	2,919	99.90	0.191436	78
80.00	0.007335	2,045			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000272	55,122	90.00	0.012318	1,218
20.00	0.000565	26,538	95.00	0.017700	847
30.00	0.001047	14,325	97.50	0.026240	572
40.00	0.001617	9,275	99.00	0.038793	387
50.00	0.002448	6,127	99.50	0.049148	305
60.00	0.003529	4,250	99.75	0.092698	162
70.00	0.005128	2,925	99.90	0.191296	78
80.00	0.007326	2,048			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

ALL INFANTS

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

	per Capita	per User
Mean	0.008812	0.009753
Standard Deviation	0.023644	0.024690
Standard Error	0.000960	0.001062

Percent of Person-Days that are User-Days = 90.35%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000165	91,135	90.00	0.027275	550
20.00	0.000198	75,706	95.00	0.037824	397
30.00	0.000663	22,623	97.50	0.044248	339
40.00	0.001535	9,771	99.00	0.061921	242
50.00	0.003103	4,835	99.50	0.104282	144
60.00	0.005439	2,758	99.75	0.219045	68
70.00	0.008047	1,864	99.90	0.325455	46
80.00	0.014200	1,056			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000006	>1,000,000	90.00	0.025879	580
20.00	0.000169	88,506	95.00	0.036697	409
30.00	0.000316	47,536	97.50	0.043562	344
40.00	0.000976	15,363	99.00	0.060663	247
50.00	0.002266	6,620	99.50	0.099759	150
60.00	0.004441	3,378	99.75	0.206791	73
70.00	0.007211	2,080	99.90	0.317880	47
80.00	0.012886	1,164			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

FEMALES (13-50 YEARS)

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.003710	0.003717
Standard Deviation	0.006874	0.006878
Standard Error	0.000068	0.000068

Percent of Person-Days that are User-Days = 99.81%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000185	80,927	90.00	0.008402	1,785
20.00	0.000361	41,541	95.00	0.012785	1,173
30.00	0.000635	23,634	97.50	0.018748	800
40.00	0.001113	13,481	99.00	0.032029	468
50.00	0.001706	8,791	99.50	0.043712	343
60.00	0.002484	6,040	99.75	0.064708	232
70.00	0.003698	4,056	99.90	0.081927	183
80.00	0.005450	2,752			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000182	82,302	90.00	0.008396	1,786
20.00	0.000358	41,844	95.00	0.012777	1,174
30.00	0.000631	23,767	97.50	0.018737	801
40.00	0.001107	13,546	99.00	0.032012	469
50.00	0.001701	8,820	99.50	0.043691	343
60.00	0.002478	6,054	99.75	0.064669	232
70.00	0.003691	4,064	99.90	0.081905	183
80.00	0.005444	2,756			

ACUTE EXPOSURE (EX4) ANALYSIS FOR BENOMYL
 Residue file name: BENOMYLA
 1989-92 DATA Adjustment factor #2 NOT used
 DPR NOEL (Acute) = 15.000000 mg/kg body-wt/day

Section 3 Registration
 Analysis date: 08-03-1999

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CUSTOM DEMOGRAPHICS 1: U.S. Population 16+ Years
 All Seasons
 All Regions
 Sex: M/F-all/
 All Races
 Age-Low: 16 yrs High: 110 yrs

Daily Exposure Analysis
 (mg/kg body-weight/day)
 per Capita per User

Mean	0.003690	0.003695
Standard Deviation	0.006493	0.006496
Standard Error	0.000040	0.000040

Percent of Person-Days that are User-Days = 99.87%

ESTIMATED PERCENTILE OF USER-DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000209	71,859	90.00	0.008574	1,750
20.00	0.000406	36,944	95.00	0.012178	1,232
30.00	0.000720	20,834	97.50	0.017077	878
40.00	0.001231	12,190	99.00	0.027912	537
50.00	0.001851	8,105	99.50	0.041364	363
60.00	0.002667	5,624	99.75	0.061299	245
70.00	0.003796	3,951	99.90	0.081492	184
80.00	0.005504	2,725			

ESTIMATED PERCENTILE OF PER-CAPITA DAYS LESS THAN/EQUAL TO CALCULATED EXPOSURE
 in mg/kg body-wt/day and corresponding Margin of Exposure (MOE)

PERCENTILE	EXPOSURE	MOE 2/	PERCENTILE	EXPOSURE	MOE
10.00	0.000206	72,720	90.00	0.008570	1,750
20.00	0.000404	37,134	95.00	0.012173	1,232
30.00	0.000717	20,918	97.50	0.017071	879
40.00	0.001227	12,230	99.00	0.027902	538
50.00	0.001847	8,122	99.50	0.041347	363
60.00	0.002663	5,633	99.75	0.061273	245
70.00	0.003792	3,956	99.90	0.081475	184
80.00	0.005499	2,728			

APPENDIX B
Chronic Dietary Exposures

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration

RESIDUE FILE NAME: BENOMYLC

ANALYSIS DATE: 08-03-1999

NFCS Combined 89-92 DATA ADJUSTMENT FACTOR #2 NOT USED

EPA Reference dose (RfD, chronic) = 0.050000 mg/kg body-wt/day

DPR NOEL (Chronic) = 15.000000 mg/kg body-wt/day

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. No PCT adjustments.

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
1	N	BLACKBERRIES	0.230000	1.00	1.00	FDAsur
2	N	BOYSENBERRIES	0.230000	1.00	1.00	FDAsur
3	N	DEWBERRIES	0.230000	1.00	1.00	FDAsur
4	N	LOGANBERRIES	0.230000	1.00	1.00	FDAsur
5	N	RASPBERRIES	0.120000	1.00	1.00	FDA
7	N	BLUEBERRIES	0.230000	1.00	1.00	FDA
10	N	CURRANTS	0.230000	1.00	1.00	FDAsur
13	N	GRAPES	0.016000	1.00	1.00	DPR
14	N	GRAPES-RAISINS	0.025000	1.00	1.00	FDA
15	N	GRAPES-JUICE	0.025000	1.00	1.00	FDA
17	N	STRAWBERRIES	0.120000	1.00	1.00	DPR
20	K	CITRUS CITRON	0.440000	1.00	1.00	FDAsur
22	K	GRAPEFRUIT-PEELED FRUIT	0.180000	1.00	1.00	FDA
23	K	GRAPEFRUIT-JUICE	0.180000	2.10	1.00	FDA
24	K	KUMQUATS	0.440000	1.00	1.00	FDAsur
26	K	LEMONS-PEELED FRUIT	0.440000	1.00	1.00	FDA
27	K	LEMONS-PEEL	0.440000	1.00	1.00	FDA
28	K	LEMONS-JUICE	0.440000	2.00	1.00	FDA
30	K	LIMES-PEELED FRUIT	0.025000	1.00	1.00	FDA-GP
31	K	LIMES-PEEL	0.025000	1.00	1.00	FDA-GP
32	K	LIMES-JUICE	0.025000	2.00	1.00	FDA-GP
33	K	ORANGES-JUICE-CONCENTRATE	0.025000	1.00	1.00	FDA-GP
34	K	ORANGES-PEELED FRUIT	0.025000	1.00	1.00	FDA-GP
35	K	ORANGES-PEEL	0.025000	1.00	1.00	FDA-GP
36	K	ORANGES-JUICE	0.025000	1.00	1.00	FDA-GP
37	K	TANGELOS	0.180000	1.00	1.00	FDAsur
38	K	TANGERINES	0.180000	1.00	1.00	FDAsur
39	K	TANGERINES-JUICE	0.180000	2.30	1.00	FDAsur
40	R	ALMONDS	0.050000	1.00	1.00	REGsur
44	R	FILBERTS (HAZELNUTS)	0.050000	1.00	1.00	REGsur
46	R	MACADAMIA NUTS (BUSH NUTS)	0.050000	1.00	1.00	REG
47	R	PECANS	0.050000	1.00	1.00	REGsur
48	R	WALNUTS	0.050000	1.00	1.00	REGsur
50	A	PISTACHIO NUTS	0.025000	1.00	1.00	REG
52	L	APPLES	0.040000	1.00	1.00	FDA-GP
53	L	APPLES-DRIED	0.040000	8.00	1.00	FDA-GP
54	L	APPLES-JUICE/CIDER	0.025000	1.00	1.00	FDA-GP
56	L	PEARS	0.025000	1.00	1.00	FDA-GP

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
57	L	PEARS-DRIED	0.025000	6.25	1.00	FDA-GP
59	M	APRICOTS	0.058000	1.00	1.00	FDA
60	M	APRICOTS-DRIED	0.058000	6.00	1.00	FDA
61	M	CHERRIES	0.052000	1.00	1.00	FDA
62	M	CHERRIES-DRIED	0.052000	4.00	1.00	FDA
63	M	CHERRIES-JUICE	0.052000	1.50	1.00	FDA
64	M	NECTARINES	0.058000	1.00	1.00	FDA
65	M	PEACHES	0.140000	1.00	1.00	FDA
66	M	PEACHES-DRIED	0.140000	7.00	1.00	FDA
67	M	PLUMS (DAMSONS)	0.083000	1.00	1.00	FDA
68	M	PLUMS-PRUNES (DRIED)	0.025000	1.00	1.00	FDA
69	M	PLUMS/PRUNE-JUICE	0.025000	1.40	1.00	FDA
72	A	BANANAS	0.025000	1.00	1.00	PDP
73	A	BANANAS-DRIED	0.025000	3.90	1.00	PDP
80	A	MANGOES	0.025000	1.00	1.00	FDA
89	A	PINEAPPLES-PEELED FRUIT	0.270000	1.00	1.00	FDA
90	A	PINEAPPLES-DRIED	0.270000	5.00	1.00	FDA
91	A	PINEAPPLES-JUICE	0.270000	1.70	1.00	FDA
141	J	CANTALOUPE-NECTAR	0.025000	1.00	1.00	DPR
142	J	CANTALOUPE-PULP (MUSKMELON)	0.025000	1.00	1.00	DPR
143	J	CASABAS	0.220000	1.00	1.00	REGsur
144	J	CRENSHAW	0.220000	1.00	1.00	REGsur
145	J	HONEYDEW MELONS	0.220000	1.00	1.00	REGsur
146	J	PERSIAN MELONS	0.220000	1.00	1.00	REGsur
147	J	WATERMELON	0.130000	1.00	1.00	REG
148	J	CUCUMBERS	0.140000	1.00	1.00	DPR
149	J	PUMPKIN	0.500000	1.00	1.00	REGsur
150	J	SQUASH-SUMMER	0.500000	1.00	1.00	REG
151	J	SQUASH-WINTER	0.500000	1.00	1.00	REGsur
154	I	EGGPLANT	0.016000	1.00	1.00	REG
155	I	PEPPERS-SWEET (GARDEN)	0.021000	1.00	1.00	REG
156	I	CHILI PEPPERS (JALAPENO)	0.021000	1.00	1.00	REG
159	I	TOMATOES-WHOLE	2.750000	1.00	1.00	REG
160	I	TOMATOES-JUICE	0.400000	1.00	1.00	REGprc
161	I	TOMATOES-PUREE	0.025000	1.00	1.00	FDA-GP
162	I	TOMATOES-PASTE	0.025000	1.00	1.00	FDA-GP
163	I	TOMATOES-CATSUP	0.070000	1.00	1.00	REGprc
166	E	CELERY	0.060000	1.00	1.00	DPR
168	F	BROCCOLI	0.025000	1.00	1.00	PDP
169	F	BRUSSELS SPROUTS	3.770000	1.00	1.00	REG
170	F	CABBAGE-GREEN AND RED	0.200000	1.00	1.00	REGsur
171	F	CAULIFLOWER	0.200000	1.00	1.00	EPA
172	F	COLLARDS	0.043000	1.00	1.00	REG
173	F	CABBAGE-CHINESE/CELERY/BOK CHO	0.200000	1.00	1.00	REG
174	F	KALE	0.200000	1.00	1.00	EPA
175	F	KOHLRABI	0.200000	1.00	1.00	EPA
183	F	MUSTARD GREENS	0.009000	1.00	1.00	REG
186	E	SPINACH	0.050000	1.00	1.00	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
198	B	CARROTS	0.086000	1.00	1.00	REG
202	D	GARLIC	0.200000	1.00	1.00	EPA
214	B	RUTABAGAS-ROOTS	0.022000	1.00	1.00	REG
218	B	SWEET POTATOES (INCLUDING YAMS	0.025000	1.00	1.00	DPR
219	B	TURNIPS-ROOTS	0.022000	1.00	1.00	REG
227	G	BEANS-DRY-GREAT NORTHERN	0.050000	1.00	1.00	REG
228	G	BEANS-DRY-KIDNEY	0.050000	1.00	1.00	REG
229	G	BEANS-DRY-LIMA	0.050000	1.00	1.00	REG
230	G	BEANS-DRY-NAVY (PEA)	0.050000	1.00	1.00	REG
231	G	BEANS-DRY-OTHER	0.050000	1.00	1.00	REG
232	G	BEANS-DRY-PINTO	0.050000	1.00	1.00	REG
233	G	BEANS-SUCCULENT-LIMA	0.040000	1.00	1.00	PDPsur
234	G	BEANS-SUCCULENT-GREEN	0.040000	1.00	1.00	PDP
235	G	BEANS-SUCCULENT-OTHER	0.040000	1.00	1.00	PDP
236	G	BEANS-SUCCULENT-YELLOW/WAX	0.040000	1.00	1.00	PDPsur
238	O	CORN/SWEET	0.025000	1.00	1.00	FDA
239	A	PEANUTS-WHOLE	0.050000	1.00	1.00	REG
249	G	BEANS-DRY-BROADBEANS	0.050000	1.00	1.00	REG
250	G	BEANS-SUCCULENT-BROADBEANS	0.040000	1.00	1.00	PDPsur
251	G	BEANS-DRY-PIGEON BEANS	0.050000	1.00	1.00	REG
253	G	BEANS-UNSPECIFIED	0.050000	1.00	1.00	REG
256	G	BEANS-DRY-HYACINTH	0.050000	1.00	1.00	REG
257	G	BEANS-SUCCULENT-HYACINTH	0.040000	1.00	1.00	PDPsur
258	G	BEANS-DRY-BLACKEYE PEAS/COWPEA	0.050000	1.00	1.00	REG
259	G	BEANS-DRY-GARBANZO/CHICK PEA	0.050000	1.00	1.00	REG
261	A	MUSHROOMS	0.040000	1.00	1.00	FDA
265	O	BARLEY	0.050000	1.00	1.00	REG
266	O	CORN/GRAIN-ENDOSPERM	0.025000	1.00	1.00	FDA
267	O	CORN/GRAIN-BRAN	0.025000	1.00	1.00	FDA
268	O	CORN SUGAR	0.025000	1.50	1.00	FDA
269	O	OATS	0.025000	1.00	1.00	REG
270	O	RICE-ROUGH (BROWN)	0.110000	1.00	1.00	REG
271	O	RICE-MILLED (WHITE)	0.110000	1.00	1.00	REG
272	O	RYE-ROUGH	0.025000	1.00	1.00	REGsur
273	O	RYE-GERM	0.025000	1.00	1.00	REGsur
274	O	RYE-FLOUR	0.025000	1.00	1.00	REGsur
276	O	WHEAT-ROUGH	0.025000	1.00	1.00	REG
277	O	WHEAT-GERM	0.025000	1.00	1.00	REGprc
278	O	WHEAT-BRAN	0.025000	1.00	1.00	REGprc
279	O	WHEAT-FLOUR	0.025000	1.00	1.00	REGprc
282	B	BEET SUGAR	0.050000	1.00	1.00	REG
289	O	CORN GRAIN-OIL	0.050000	1.00	1.00	FDA
293	A	PEANUTS-OIL	0.050000	1.00	1.00	REG
297	G	SOYBEANS-OIL	0.025000	1.00	1.00	REG
304	G	SOYBEANS-MATURE SEEDS DRY	0.025000	1.00	1.00	REG
305	G	SOYBEANS-FLOUR (FULL FAT)	0.025000	1.00	1.00	REG
306	G	SOYBEANS-FLOUR (LOW FAT)	0.025000	1.00	1.00	REG
307	G	SOYBEANS-FLOUR (DEFATTED)	0.025000	1.00	1.00	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
315	A	GRAPES-WINE AND SHERRY	0.016000	1.00	1.00	DPR
318	X	MILK-NONFAT SOLIDS	0.001200	1.00	1.00	REGTAS
319	X	MILK-FAT SOLIDS	0.005800	1.00	1.00	REGTAS
320	X	MILK SUGAR (LACTOSE)	0.002600	1.00	1.00	REGTAS
321	U	BEEF-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
322	U	BEEF(ORGAN MEATS)-OTHER	0.075000	1.00	1.00	REGTAS
323	U	BEEF-DRIED	0.000400	1.92	1.00	REGTAS
324	U	BEEF(BONELESS)-FAT	0.000700	1.00	1.00	REGTAS
325	U	BEEF(ORGAN MEATS)-KIDNEY	0.004500	1.00	1.00	REGTAS
326	U	BEEF(ORGAN MEATS)-LIVER	0.007500	1.00	1.00	REGTAS
327	U	BEEF(BONELESS)-LEAN (FAT/FREE)	0.000400	1.00	1.00	REGTAS
328	U	GOAT-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
329	U	GOAT(ORGAN MEATS)-OTHER	0.075000	1.00	1.00	REGTAS
330	U	GOAT(BONELESS)-FAT	0.000700	1.00	1.00	REGTAS
331	U	GOAT(ORGAN MEATS)-KIDNEY	0.004500	1.00	1.00	REGTAS
332	U	GOAT(ORGAN MEATS)-LIVER	0.075000	1.00	1.00	REGTAS
333	U	GOAT(BONELESS)-LEAN (FAT/FREE)	0.000400	1.00	1.00	REGTAS
334	U	HORSE	0.000400	1.00	1.00	REGTAS
336	U	SHEEP-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
337	U	SHEEP(ORGAN MEATS)-OTHER	0.075000	1.00	1.00	REGTAS
338	U	SHEEP(BONELESS)-FAT	0.000700	1.00	1.00	REGTAS
339	U	SHEEP(ORGAN MEATS)-KIDNEY	0.004500	1.00	1.00	REGTAS
340	U	SHEEP(ORGAN MEATS)-LIVER	0.075000	1.00	1.00	REGTAS
341	U	SHEEP(BONELESS)-LEAN (FAT FREE)	0.000400	1.00	1.00	REGTAS
342	U	PORK-MEAT BYPRODUCTS	0.013000	1.00	1.00	REGTAS
343	U	PORK(ORGAN MEATS)-OTHER	0.013000	1.00	1.00	REGTAS
344	U	PORK(BONELESS)-FAT	0.000100	1.00	1.00	REGTAS
345	U	PORK(ORGAN MEATS)-KIDNEY	0.000800	1.00	1.00	REGTAS
346	U	PORK(ORGAN MEATS)-LIVER	0.013000	1.00	1.00	REGTAS
347	U	PORK(BONELESS)-LEAN (FAT FREE)	0.000100	1.00	1.00	REGTAS
355	V	TURKEY-BYPRODUCTS	0.002100	1.00	1.00	REGTAS
356	V	TURKEY-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
357	V	TURKEY-(BONELESS)-FAT	0.002100	1.00	1.00	REGTAS
358	V	TURKEY-(BONELESS)LEAN/FAT FREE	0.000050	1.00	1.00	REGTAS
359	V	TURKEY-UNSPECIFIED	0.002100	1.00	1.00	REGTAS
360	V	POULTRY-OTHER-LEAN (FAT FREE)	0.000050	1.00	1.00	REGTAS
361	V	POULTRY-OTHER-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
362	V	POULTRY-OTHER-FAT	0.002100	1.00	1.00	REGTAS
363	X	EGGS-WHOLE	0.002000	1.00	1.00	REGTAS
364	X	EGGS-WHITE ONLY	0.002000	1.00	1.00	REGTAS
365	X	EGGS-YOLK ONLY	0.002000	1.00	1.00	REGTAS
366	V	CHICKEN-BYPRODUCTS	0.002100	1.00	1.00	REGTAS
367	V	CHICKEN-GIBLETS (LIVER)	0.002100	1.00	1.00	REGTAS
368	V	CHICKEN (BONELESS)-FAT	0.002100	1.00	1.00	REGTAS
369	V	CHICKEN(BONELESS)LEAN/FAT FREE	0.000050	1.00	1.00	REGTAS
377	L	APPLES-JUICE-CONCENTRATE	0.025000	1.00	1.00	FDA-GP
378	A	BANANAS-NECTAR	0.025000	1.00	1.00	PDP
379	B	BEEET SUGAR-MOLASSES	0.050000	1.00	1.00	REG

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
380	N	BLACKBERRIES-JUICE	0.230000	1.00	1.00	FDAsur
383	F	CABBAGE-SAVOY	0.200000	1.00	1.00	EPA
384	E	CELERY JUICE	0.060000	1.00	1.00	DPR
385	V	CHICKEN-GIBLETS (EXCL. LIVER)	0.002100	1.00	1.00	REGTAS
388	O	CORN SUGAR-MOLASSES	0.025000	1.50	1.00	FDA
392	N	GRAPES-JUICE-CONCENTRATE	0.025000	1.00	1.00	FDA-GP
398	X	MILK-BASED WATER	0.001200	1.00	1.00	REGTAS
399	O	OATS-BRAN	0.025000	1.00	1.00	REG
402	M	PEACHES-JUICE	0.140000	1.00	1.00	FDA
403	A	PEANUT-BUTTER	0.050000	1.89	1.00	REG
404	L	PEARS-NECTAR	0.025000	1.00	1.00	FDA-GP
406	A	PINEAPPLES-JUICE-CONCENTRATE	0.270000	1.00	1.00	FDA
408	O	RICE-BRAN	0.110000	1.00	1.00	REG
409	O	RICE-WILD	0.110000	1.00	1.00	REG
410	M	APRICOT JUICE OR NECTAR	0.058000	1.00	1.00	FDA
416	N	STRAWBERRIES-JUICE	0.120000	1.00	1.00	DPR
420	K	TANGERINES-JUICE-CONCENTRATE	0.180000	7.35	1.00	FDAsur
423	I	TOMATOES-DRIED	2.750000	14.30	1.00	REG
424	U	VEAL- (BONELESS) -FAT	0.000700	1.00	1.00	REGTAS
425	U	VEAL- (BONELESS) -LEAN (FAT FREE	0.000400	1.00	1.00	REGTAS
426	U	VEAL- (ORGAN MEATS) -KIDNEY	0.004500	1.00	1.00	REGTAS
427	U	VEAL- (ORGAN MEATS) -LIVER	0.075000	1.00	1.00	REGTAS
428	U	VEAL- (ORGAN MEATS) -OTHER	0.075000	1.00	1.00	REGTAS
429	U	VEAL-DRIED	0.000400	1.92	1.00	REGTAS
430	U	VEAL-MEAT BYPRODUCTS	0.075000	1.00	1.00	REGTAS
436	J	WATERMELON-JUICE	0.130000	1.00	1.00	REG
437	O	WHEAT-GERM OIL	0.025000	1.00	1.00	REGprc
441	K	GRAPEFRUIT-JUICE-CONCENTRATE	0.180000	8.26	1.00	FDA
442	K	LEMONS-JUICE-CONCENTRATE	0.440000	11.40	1.00	FDA
443	K	LIMES-JUICE-CONCENTRATE	0.025000	6.00	1.00	FDA
448	K	GRAPEFRUIT PEEL	0.180000	1.00	1.00	FDA
449	V	TURKEY- (ORGAN MEATS) -OTHER	0.002100	1.00	1.00	REGTAS
940	A	PEANUTS HULLED	0.050000	1.00	1.00	REG

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration

RESIDUE FILE NAME: BENOMYLC

ANALYSIS DATE: 08-03-1999

NFCS Combined 89-92 DATA ADJUSTMENT FACTOR #2 NOT USED

EPA Reference dose (RfD, chronic) = 0.050000 mg/kg body-wt/day

DPR NOEL (Chronic) = 15.000000 mg/kg body-wt/day

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. No PCT adjustments.

TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE		
	mg/kg body-wt/day	Margin of Exposure 1/	Percent of RfD
U.S. POP - 48 STATES - ALL SEASONS	0.001838	8,161	3.7%
U.S. POPULATION - SPRING SEASON	0.001740	8,621	3.5%
U.S. POPULATION - SUMMER SEASON	0.002025	7,407	4.1%
U.S. POPULATION - AUTUMN SEASON	0.001815	8,263	3.6%
U.S. POPULATION - WINTER SEASON	0.001752	8,560	3.5%
NORTHEAST REGION	0.001964	7,637	3.9%
MIDWEST REGION	0.001670	8,984	3.3%
SOUTHERN REGION	0.001824	8,223	3.6%
WESTERN REGION	0.001936	7,750	3.9%
PACIFIC REGION	0.001984	7,559	4.0%
HISPANICS	0.002104	7,128	4.2%
NON-HISPANIC WHITES	0.001835	8,175	3.7%
NON-HISPANIC BLACKS	0.001594	9,409	3.2%
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.002210	6,786	4.4%
ALL INFANTS	0.001602	9,365	3.2%
NURSING INFANTS (<1 YEAR OLD)	0.000704	21,299	1.4%
NON-NURSING INFANTS (<1 YEAR OLD)	0.001979	7,578	4.0%
CHILDREN (1-6 YEARS)	0.003223	4,655	6.4%
CHILDREN (7-12 YEARS)	0.002668	5,622	5.3%
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.001777	8,439	3.6%
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.001589	9,438	3.2%
FEMALES (13-50 YEARS)	0.001568	9,567	3.1%
FEMALES (13+/PREGNANT/NOT NURSING)	0.001418	10,577	2.8%
FEMALES (13+/NURSING)	0.001690	8,873	3.4%
MALES (13-19 YEARS)	0.001655	9,064	3.3%
MALES (20+ YEARS)	0.001534	9,780	3.1%
SENIORS (55+)	0.001596	9,401	3.2%

1. Margin of Exposure = DPR NOEL / Dietary Exposure

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration

RESIDUE FILE NAME: BENOMYLC

ANALYSIS DATE: 08-03-1999

NFCS Combined 89-92 DATA ADJUSTMENT FACTOR #2 NOT USED

Q* = 0.004300

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. No PCT adjustments.

 TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE	
	mg/kg body-wt/day	Life-Time Risk (Q1=0.004300)
U.S. POP - 48 STATES - ALL SEASONS	0.001838	7.90E-06
U.S. POPULATION - SPRING SEASON	0.001740	7.48E-06
U.S. POPULATION - SUMMER SEASON	0.002025	8.71E-06
U.S. POPULATION - AUTUMN SEASON	0.001815	7.81E-06
U.S. POPULATION - WINTER SEASON	0.001752	7.54E-06
NORTHEAST REGION	0.001964	8.45E-06
MIDWEST REGION	0.001670	7.18E-06
SOUTHERN REGION	0.001824	7.84E-06
WESTERN REGION	0.001936	8.32E-06
PACIFIC REGION	0.001984	8.53E-06
HISPANICS	0.002104	9.05E-06
NON-HISPANIC WHITES	0.001835	7.89E-06
NON-HISPANIC BLACKS	0.001594	6.85E-06
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.002210	9.50E-06
ALL INFANTS	0.001602	6.89E-06
NURSING INFANTS (<1 YEAR OLD)	0.000704	3.03E-06
NON-NURSING INFANTS (<1 YEAR OLD)	0.001979	8.51E-06
CHILDREN (1-6 YEARS)	0.003223	1.39E-05
CHILDREN (7-12 YEARS)	0.002668	1.15E-05
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.001777	7.64E-06
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.001589	6.83E-06
FEMALES (13-50 YEARS)	0.001568	6.74E-06
FEMALES (13+/PREGNANT/NOT NURSING)	0.001418	6.10E-06
FEMALES (13+/NURSING)	0.001690	7.27E-06
MALES (13-19 YEARS)	0.001655	7.12E-06
MALES (20+ YEARS)	0.001534	6.60E-06
SENIORS (55+)	0.001596	6.86E-06

Chronic Exposure (EX1) Analysis for Benomyl

Section 3 Registration

RESIDUE FILE NAME: BENOMYLC

ANALYSIS DATE: 08-03-1999

NFCS Combined 89-92 DATA ADJUSTMENT FACTOR #2 NOT USED

Q* = 0.006700

COMMENT 1: EPA tolerances + DPR, FDA, USDA-PDP, & Registrant residue values

COMMENT 2: CSFII consumption database. No PCT adjustments.

 TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE	
	mg/kg body-wt/day	Life-Time Risk (Q*=0.006700)
U.S. POP - 48 STATES - ALL SEASONS	0.001838	1.23E-05
U.S. POPULATION - SPRING SEASON	0.001740	1.17E-05
U.S. POPULATION - SUMMER SEASON	0.002025	1.36E-05
U.S. POPULATION - AUTUMN SEASON	0.001815	1.22E-05
U.S. POPULATION - WINTER SEASON	0.001752	1.17E-05
NORTHEAST REGION	0.001964	1.32E-05
MIDWEST REGION	0.001670	1.12E-05
SOUTHERN REGION	0.001824	1.22E-05
WESTERN REGION	0.001936	1.30E-05
PACIFIC REGION	0.001984	1.33E-05
HISPANICS	0.002104	1.41E-05
NON-HISPANIC WHITES	0.001835	1.23E-05
NON-HISPANIC BLACKS	0.001594	1.07E-05
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.002210	1.48E-05
ALL INFANTS	0.001602	1.07E-05
NURSING INFANTS (<1 YEAR OLD)	0.000704	4.72E-06
NON-NURSING INFANTS (<1 YEAR OLD)	0.001979	1.33E-05
CHILDREN (1-6 YEARS)	0.003223	2.16E-05
CHILDREN (7-12 YEARS)	0.002668	1.79E-05
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.001777	1.19E-05
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.001589	1.06E-05
FEMALES (13-50 YEARS)	0.001568	1.05E-05
FEMALES (13+/PREGNANT/NOT NURSING)	0.001418	9.50E-06
FEMALES (13+/NURSING)	0.001690	1.13E-05
MALES (13-19 YEARS)	0.001655	1.11E-05
MALES (20+ YEARS)	0.001534	1.03E-05
SENIORS (55+)	0.001596	1.07E-05

APPENDIX F

PEER REVIEW COMMENTS AND RESPONSE

Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director

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Winston H. Hickox
Secretary for
Environmental
Protection



Gray Davis
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1020 N Street
Sacramento, CA 95814-5624

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
2151 Berkeley Way, Annex 11
Berkeley, California 94704

DATE: January 19, 1999

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S
DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE
INGREDIENT BENOMYL

We have completed our review of the draft risk characterization document (RCD) for benomyl prepared by the Department of Pesticide Regulation (DPR). Benomyl is a systemic fungicide of the benzimidazole class that is used for the control of a wide-range of fungal diseases. In California, the majority of benomyl is used on almonds, celery, grapes, stone fruits, and strawberries. Benomyl is also used as a seed treatment, for bulb dips and by homeowners on garden vegetables/fruits and lawns. In 1994, 150,000 or more pounds of the active ingredient were used in California. The draft RCD states that benomyl entered the risk assessment process because of teratogenicity, oncogenicity, reproductive toxicity, and adverse effects on the liver caused by chronic exposure. Benomyl is a high priority active ingredient under the Birth Defect Prevention Act of 1984 (SB 950) and also is a candidate for evaluation under the Toxic Air Contaminant Identification and Control Act of 1983 (AB 1807).

The draft RCD package submitted to the Office of Environmental Health Hazard Assessment (OEHHA) consists of the draft RCD (May 26, 1998) prepared by the Medical Toxicology Branch and three appendices as well as a summary of toxicology data for benomyl (last revised on October 1, 1997). A draft exposure assessment (November 7, 1996) prepared by

California Environmental Protection Agency



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Gary T. Patterson, Ph.D., Chief
January 19, 1999
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the Worker Health and Safety Branch was submitted as appendix A. Appendix B is an oncogenicity dose-response model and appendix C includes the commodity residue values.

It is not clear from reviewing the draft RCD whether there was a complete search of the open literature to identify relevant articles on the toxicology, mechanism of action, and pharmacokinetics of benomyl and its major breakdown products. All pertinent information published in the open literature, in addition to information submitted by the registrant, should be considered in preparing a risk assessment for any pesticide active ingredient. If a complete search was conducted, and no relevant data were identified, we recommend that this be made clear in the benomyl RCD before it is finalized. We have included some citations to articles found in the open literature that might be useful in revising the draft RCD (see attached comments).

The comments that follow are grouped according to the headings used in the RCD. Please note that although a comment may appear under a specific heading, its impact may not be limited to that specific section; it may have relevance to other sections of the RCD. Based on our review of the draft RCD for benomyl, we feel that the document needs significant revision before finalization. In general, the assumptions and conclusions stated in the draft RCD require more scientific support, additional analysis, and more detailed discussion in order to provide a complete characterization of the risks posed by the use of benomyl in California. We would be interested in discussing our comments and conclusions with your staff.

Thank you for the opportunity to comment on the draft RCD for benomyl. If you have any questions about our comments, please contact me or Dr. Michael DiBartolomeis at (510) 622-3200.

cc: Joan E. Denton, Ph.D., Director, OEHHA
Val Siebal, Chief Deputy Director, OEHHA
George V. Alexeeff, Ph.D., Deputy Director, OEHHA
Michael J. DiBartolomeis, Ph.D., PETS/OEHHA

GENERAL COMMENTS

The draft risk characterization document for benomyl includes a summary and critique of the data available in DPR's registration database on the active ingredient and parent compound benomyl. We found the inclusion of summary tables helpful in accessing some of the more critical information.

It is not clear from reviewing the draft RCD whether there was a complete search of the open literature to identify relevant articles on the toxicology, mechanism of action, and pharmacokinetics of benomyl and its major breakdown products. All pertinent scientific information published in the open literature, in addition to information submitted by the registrant, should be considered in preparing a risk assessment for any pesticide active ingredient. In this regard, the literature on an important public health issue concerning benomyl, the potential for benomyl to cause anophthalmia (a birth defect resulting in no eyes), should be discussed (see more detailed comment below).

Of major concern is the omission of a characterization of exposure and risk for the predominant breakdown product of benomyl, butyl isocyanate (BIC). Although the compound is identified in the exposure assessment (appendix A) as a breakdown product of benomyl, neither release nor exposure to this compound are discussed or quantified despite its high toxicity (Pauluhn and Eben, Arch. Toxicol. 66:118-125, 1992). Page five of appendix A describes this chemical as a cholinesterase inhibitor "equivalent in potency to some organophosphates." It would be more accurate to characterize BIC as a highly irritating volatile organic compound that is a potent inhibitor of several important enzymes. The time-course of release of this potential toxic air contaminant after benomyl application and the resulting levels in ambient air cannot be determined from the information provided. We recommend that the draft RCD be revised to include a complete discussion and evaluation of the health risk information available regarding exposure to BIC from the use of benomyl in California.

The draft RCD would be improved with significant editing and reorganization. For example, the document would be enhanced by modifying appendix C (see comments below for some suggestions); and including greater detail on the methods, results, and assumptions described in the exposure assessment, particularly on the use of the Pesticide Handlers Exposure Database and the TAS exposure software. The tolerance assessment section could be moved to precede the risk appraisal section. In addition, the descriptions of reproductive and developmental toxicity studies and the subchronic studies could be combined with observed reproductive and developmental toxicity to emphasize the large body of evidence for the reproductive and developmental toxicity of benomyl. The document also needs to be checked for spelling errors.

Toxicology Profile

This is a relatively lengthy section that describes in summary format a large amount of data on the active ingredient and parent compound benomyl and data for the metabolite methyl 2-benzimidazolecarbamate (MBC). The summary of toxicology for benomyl was also included which contains summaries of the data submitted for registration. In some cases there are differences in the information presented in the two documents that may lead to questions of data interpretation that should either be corrected, or noted and explained in the revised RCD (see specific comments below for reproductive toxicity).

Breakdown products and metabolites. A toxicological profile for butyl isocyanate (BIC), the major environmental breakdown product of benomyl, is not included in this section of the draft RCD. We recommend that the draft RCD be revised to include a summary of the toxicity of BIC, including the determination of the critical dose (i.e., NOAEL or LOAEL) for risk assessment. Other breakdown products as well as metabolites (see for example the section on pharmacokinetics) should also be identified, accompanied by a brief discussion of the known toxicology of these compounds. A flow diagram showing the pathways of benomyl metabolism and breakdown in the environment with the chemical structures of the compounds would be a good way to address this. We acknowledge the inclusion on page eight of the two formulae for benomyl and the metabolite methyl 2-benzimidazolecarbamate (MBC). This could be expanded to include the other breakdown products and metabolites.

Administered doses. Information on the actual administered dose of benomyl to laboratory animals in dietary, drinking water, or inhalation studies is missing from the summaries of many of the experimental studies described in this section. For example, the FAO (1985) study states that the NOEL for body weight loss was 150 ppm, but no calculation was provided as to the administered dose level (in mg/kg-day). Administered dose levels were also not given for Sherman (1969b), Sherman (1972b) (rats), Warheit et al. (1989), Barnes et al. (1983), Haskell (1972), and others. Comparing results for the different studies is not possible without knowledge of the administered doses and we recommend that the document be revised to provide this information to the reader.

Reproductive toxicity. The 1968 three-generation reproductive study in rats (Sherman, 1968) is a pivotal study. The U.S. Environmental Protection Agency (U.S. EPA) in 1997 based its reference dose (RfD) of 0.05 mg/kg-day on the NOEL (5 mg/kg-day) for decreased weanling weight at the next highest dose from this study. The draft RCD concludes that the study is "not acceptable under FIFRA guidelines" for risk assessment for inadequate group size and lack of feed analysis. However, Food and Agriculture Code 14022(C) states that "the Director shall consider all available scientific data" for the TAC program. From another relevant study by Barnes et al. (1983), a LOEL of 203 ppm (10 mg/kg-day?) for decreases in male reproductive parameters

might be identified. However, the draft RCD selected a NOEL of 28.2 mg/kg-day from a different study (Mebus, 1991) on testicular parameters for risk assessment. The draft RCD does not provide enough information to assess the validity of this determination. Based on the information available, we cannot determine if the justification for not using the Sherman (1968) and the Barnes et al. (1983) studies for risk assessment is sufficient. We recommend that the RCD be revised to include a detailed description of the study designs and results and a summary of U.S. EPA's determinations and conclusions. Further justification would likely be needed to support the determination that a higher NOEL from another study for comparable effects in offspring should be used instead of the lower NOEL in the Sherman (1968) study for effects on weanlings.

Genotoxicity. The inclusion of a large number of genotoxicity studies for benomyl and MBC in the draft RCD is noted. However, the summary of the studies does not accurately describe the weight of evidence. When considering the body of evidence for genotoxicity, a better scientific approach would be to weigh the effects from all studies submitted by the registrants and those published in the peer reviewed literature, regardless of whether they are "acceptable" according to FIFRA or TSCA guidelines. We agree that the results are mostly negative for the mutagenicity of purified benomyl (95% or greater). However, the results are equivocal for the mutagenicity of benomyl of lesser purity (50%) and for the breakdown product MBC. The number of positive studies for chromosomal aberrations for purified benomyl (95% or greater) with or without metabolic activation cannot be dismissed, and these data suggest that benomyl is genotoxic. We recommend that the summary paragraph be revised to more accurately reflect the results from all studies. The final conclusion should be revised to read "Considering all of the data, the equivocal results in gene mutation testing and the positive results in chromosomal aberration tests suggest that benomyl and MBC (or an impurity that is not always present) possess some genotoxic activity."

Risk Assessment (Hazard Identification)

Selection of NOEL for acute exposure. A NOEL of 10 mg/kg MBC (15 mg/kg in benomyl equivalents) for post-implantation loss observed in a developmental study in rabbits (Feussner, 1985) was selected for the estimation of acute margins of exposure in the draft RCD. This was based on the fact that there was no significant increase in the number of litters with at least one resorption in the 10 mg/kg group (low dose) versus the controls (3/14 compared to 4/16 in the controls and the low dose group, respectively). The number of resorptions, however, in the 10 mg/kg group (16/119) was significantly increased versus that observed in the controls (3/108). The draft RCD supports the conclusion that 10 mg/kg is a NOEL by stating "the best estimate of biological effects is obtained using the litter as the unit for comparison." This is not sufficient scientific justification as to why the litter is a better measure of effects than are the number of fetal resorptions. Additionally, since there is clearly a dose-related trend in the number of resorptions,

10 mg/kg may be a LOEL rather than a NOEL. We suggest the reevaluation of the data comparing the number of resorptions per litter as a function of dose, thus incorporating both individual and litter data into the analysis. If no further justification can be provided for using litter data rather than resorption data, we recommend that 10 mg/kg be considered a LOEL and the appropriate modification made to the risk assessment.

Selection of NOEL for chronic exposure. A chronic NOEL of 15 mg/kg-day for hepatotoxicity (cirrhosis, fatty liver, increased serum liver enzymes) was identified in a two-year benomyl feeding study in dogs (Sherman, 1970). A lower NOEL of 7.4 mg/kg-day benomyl equivalents based on hepatotoxicity (pericholangitis/cholangiohepatitis) was identified in a two-year feeding study in rats (Sherman, 1972b). The latter study, however, was determined in the draft RCD to be unacceptable according to FIFRA guidelines due to lack of feed analysis and inadequate animal group size. However, the feed analysis problem appears to have been resolved (see Summary of Toxicology Data for Benomyl, 10/1/97). Furthermore, although the group size was 36 animals/dose, numbers that might not meet FIFRA guidelines, the size of the study should be adequate for risk assessment purposes since toxicity was observed.

As mentioned above, and on page 39 of the draft RCD, U.S. EPA identified a NOEL of 5 mg/kg-day based on decreased weanling weights from a three-generation rat reproduction study (Sherman, 1968). The draft RCD selected a NOEL based on hepatotoxicity from a different study that is three times higher (and therefore less health-protective) than U.S. EPA's NOEL. The rationale stated in the document is that the "study [from which U.S. EPA selected its NOEL] was not acceptable to DPR under FIFRA guidelines because of inadequate group size and lack of feed analysis despite demonstrable instability of the test article." Although there might be a regulatory basis for disregarding these data, the disagreement with U.S. EPA's selected NOEL needs further explanation and justification in the risk assessment. We reviewed the basis for the selection of the NOEL of 5 mg/kg-day by U.S. EPA and conclude that the use of this NOEL for risk assessment is not fully justified by the data (there was no effect on weanling weights at the highest dose; no dose-response was established). A comparable scientific explanation should be included in this section of the RCD to support the selection of an alternative NOEL.

Based on the available data and the severity of the adverse liver effects found in several studies, we recommend that the chronic NOEL for use in the risk assessment for benomyl be 7.4 mg/kg-day and not 15 mg/kg-day as used in the draft RCD. We also recommend that a scientific explanation for deviation from U.S. EPA's NOEL be included in the revised RCD.

Oncogenicity. Based on the summary information provided in the draft RCD, we agree that the Wiechman (1982) study is more appropriate for use in risk assessment than the Wood (1982) study used by U.S. EPA as the basis for the quantification of benomyl's carcinogenic potency. An additional factor supporting the use of Wiechman (1982) is that the study was conducted with

benomyl instead of MBC, which was used in the study by Wood (1982). However, insufficient information was given to verify the accuracy of the human cancer potency factor derived in the draft RCD. The text states that the animal potency (which was verified using the mstage model), derived from the data using Global 86 was scaled using the factor: (body weight)^{3/4}. The animal and human body weights used in the draft RCD to perform this calculation were not presented in the text (OEHHA assumes that 70 kg and 0.03 kg were used for human and mouse, respectively). The default body weight values should be provided in the revised RCD so that the calculations can be reproduced.

Epidemiological data. Available information on benomyl exposures and potential eye malformations was not discussed in the RCD. This subject was introduced into the literature by a report on clusters of anophthalmia and microphthalmia (microscopic eyes and blindness) in the UK that was associated with exposure to benomyl. Benomyl was considered a suspect chemical because of its similar effects in animal studies. This attracted public attention and concern that culminated in a lawsuit in Florida over microphthalmia in a child born to a woman who reported exposure to Benlate in the first trimester. The verdict found the pesticide manufacturer liable for damages. However, several epidemiological studies, which are apparently more definitive than the original report, do not support an association between anophthalmia and benomyl (see, for instance, *Reprod. Toxicol.* 8:397-403, 1994; *Brit. Med. J.* 308:205, 1994; *Brit. Med. J.* 308:205-206, 1994). This topic should be discussed in the benomyl RCD to acknowledge such concerns as expressed in the article by A. Watterson, "Pesticide reproductive health hazards in humans and public health policy options: some unanswered questions and undocumented answers arising from the benomyl debate," in *J. Public Health Med.* 16:141-144, 1994.

Risk Assessment (Exposure Assessment)

Inclusion of 2-[methoxycarbonylamino]-benzimidazole (MBC). MBC, one of the primary metabolites of benomyl, is assumed to be responsible for the majority of toxic effects observed following benomyl exposure. Toxicity data on MBC, after molecular weight adjustment, are considered in the draft RCD to be applicable to the assessment of benomyl risks (see page 38 for example). The draft RCD only considers benomyl and MBC derived from benomyl use in the exposure assessment. This would be appropriate if MBC was exclusively a byproduct of the metabolism of benomyl. However, there are other occupational and dietary sources of MBC. For example, thiophanate-methyl, another fungicide, is degraded and metabolized to MBC. MBC, although no longer registered for use in California, is manufactured and used as a fungicide known as carbendazim. MBC residues from the use of MBC may also contribute to the "benomyl/MBC" dietary exposure. Likewise, MBC residues from the use of compounds such as thiophanate-methyl may contribute to both the dietary and occupational "benomyl/MBC" exposures. These potential sources should be discussed and if possible quantified in the exposure assessment (e.g., appendix A) and incorporated into the assessment of margins of safety. If this is

not possible due to inadequate data, a discussion on uncertainty should include the degree to which this omission would underestimate risks.

Inclusion of other structurally similar fungicides in the exposure assessment. To complete the risk characterization, a discussion regarding any oncogenic potential from other benzimidazole compounds would be useful.

Home use exposure assessment. The text of appendix A states that no exposure assessment was performed for this scenario. However, in the body of the draft RCD, exposure and risk estimates are given for this use. This apparent inconsistency needs to be corrected by continuing to include the home use scenario in the RCD and replacing the inconsistent text in appendix A. The rationale given in appendix A for not estimating the exposure for home applications is that it is expected that benomyl will not be available for home use within the next two years. This assumption cannot be verified or guaranteed. Therefore, until the registration for this use of benomyl is actually cancelled, we recommend that the home uses of this active ingredient continue to be characterized.

Dietary exposure estimates. Dietary exposure analyses were conducted using Exposure-1 and Exposure-4 software. Little detail regarding the assumptions in using this software was provided in the text of the draft RCD and we recommend including a more detailed explanation of the assumptions used.

Combined Occupational and Dietary Exposure. It is not clear why the population subgroup, women 20+ years of age, was chosen to estimate the combined exposure. The rationale provided in the draft RCD is that occupational exposures were derived from agricultural workers for this subpopulation. The text suggests, however, that all of the occupational exposures were estimated for men, with the exception of field workers. The legend of Table 15 (which gives the combined exposures) also states a body weight of 75.9 kg was assumed for all work tasks by field workers and home gardeners (the activities associated with the greatest exposure). This is the body weight used in the draft RCD for men, not women. This apparent discrepancy needs to be clarified.

Risk Assessment (Risk Characterization)

Margins of exposure. MOE calculations for several scenarios were checked and found to be mathematically correct. As calculated in the draft RCD based on the draft assumptions, exposure estimates, and interpretation of the data, all acute MOEs are greater than 100, a level stated in the draft RCD as being "the value conventionally recommended to protect people from the toxic effects of a chemical." However, some MOEs are relatively small (e.g., 200 to 300). If the acute NOEL of 10 mg/kg MBC (15 mg/kg in benomyl equivalents) for post-implantation loss observed

in a developmental study in rabbits was selected as a LOEL rather than a NOEL as we recommend, these MOEs would be 10-fold lower, or less than 100. In addition, changes in some of the assumptions and approaches used in the exposure assessment could further decrease the MOEs. The same concerns could apply to the chronic MOEs although they are significantly higher (all are 3,000 or greater) and the resultant impact would not be as significant for public health protection. We recommend that a quantitative discussion of the uncertainties in conducting the risk assessment for noncancer endpoints be included in the revised RCD. This would include a quantification of the impact of using upper-bound rather than average exposure calculations in the exposure assessment.

Cancer risks. Risk calculations for several scenarios were checked and found to be mathematically correct. Most of the estimated cancer risks exceed 1×10^{-6} , several do so by an order of magnitude (e.g., 14×10^{-6} for wine grape field workers). As for the noncancer effects assessment, we recommend that a quantitative discussion of the uncertainties in conducting the cancer risk assessment for benomyl be included in the revised RCD.

Risk Appraisal

The risk appraisal is a predominantly qualitative discussion of the uncertainty in the risk assessment for benomyl. The current discussion addresses several areas of uncertainty associated with the selection of a NOEL and the assessment of exposure. Nevertheless, we recommend that this section be revised considering our recommendations for additional uncertainty analysis as noted in our comments above.

Use of gloves for residential exposures. Although the majority of the subjects in the surrogate study used to estimate exposure to benomyl from home uses did not wear gloves, it was assumed for the purposes of this risk assessment that the home users of benomyl wear gloves. A more health-protective approach (which also is apparently more consistent with the study) to use when data do not exist on the general population is to assume that home users would not be wearing gloves. We recommend that the exposures be recalculated based on the assumption that persons would not wear gloves during home use of benomyl, or that data on both conditions be provided.

Federal Food Quality Protection Act. The requirement of the FQPA to account for potential pre- and post-natal developmental toxicity and the completeness of the database with respect to exposure and toxicity to infants and children was discussed in the draft RCD. The document further points out that the regulatory endpoint used in the RCD for calculating MOEs for daily exposure is based on a developmental endpoint. No decision is made, however, with regard to whether an additional safety factor/margin of safety needs to be considered for the protection of infants and children from toxicity due to benomyl exposure. This is a science-based decision and

should be resolved in the risk assessment. We determine from the data reviewed in the draft RCD that based on the FQPA criteria, an additional 10-fold uncertainty factor would be justified.

Potential endocrine effects (mechanism of action of female reproductive effects) and cumulative and aggregate exposure (degree of underestimation by not including aggregate or cumulative exposures) need to be addressed in greater detail in this section of the RCD. In addition, other relevant studies on developmental effects of benomyl should be discussed (Ellis et al., *Teratog. Carcinog. Mutagen* 7:357-375, 1998; Ellis et al., *Teratog. Carcinog. Mutagen* 8:377-391, 1988; Hoogenboom et al., *Curr. Eye Res.* 10:601-612, 1991; Kavlock et al., *Toxicol. Appl. Pharmacol.* 62:44-54, 1982; Sherman et al., *Toxicol. Appl. Pharmacol.* 32:305-315, 1975; Zeman et al., *J. Toxicol. Environ. Health* 17:405-417, 1986).

Illness Reports. The relationship of exposures, as estimated in the draft exposure assessment, and the illnesses as separately documented in DPR's pesticide illness surveillance program and reported on page six of the draft RCD, is not clear. Information given by Koehler and Moye (1995) on airborne insecticide residue may be of significance. We recommend reviewing this paper and including a discussion about the relationship between exposures and documented illness reports in the revised RCD. Alternatively, a statement in this section stating that based on the occurrence of illness attributed to benomyl exposure, the MOEs calculated in the RCD might be underestimated for some exposures under certain conditions of primarily occupational use.

Tolerance Assessment

It is not clear how the tolerance assessment was performed. For example, a range of MOEs for several commodities is presented for "each population subgroup." Population subgroups are not defined in this section however. It should be clarified as to whether these are the same population subgroups used for the dietary assessment presented earlier in the document. We note that MOEs were less than 100 for several commodities including apples, grapes, oranges, pears, peaches, and pineapples.

Appendix A, Exposure Assessment Prepared by the Worker Health and Safety Branch

Use of the "Pesticide Handlers Exposure Database" to estimate exposure data. Several limitations regarding the use of the Pesticide Handlers Exposure Database are given in the document and together they provide strong support for not using the Pesticide Handlers Exposure Database for exposure estimation. For instance, the physical properties of the pesticide are not included as selection criteria for the database. This is an important limitation of this approach since physical properties of a chemical (e.g., vapor pressure) can significantly influence occupational exposure. Also in the document, an exposure study with benomyl is briefly discussed, but dismissed due to limitations of study duration and patch size (Everhart and Holt,

1982). The use of exposure data from a benomyl study in humans (with appropriate adjustment) would appear to be better than using the exposure data from the Pesticide Handlers Exposure Database and we recommend evaluating exposures based on the human study. Another option is to provide exposure estimates based on both approaches, and weighing the advantages and disadvantages of each approach. A new study that has been published since the completion of this exposure assessment in 1996 would be useful to incorporate (Heekstra et al., J. Occup. Environ. Med 38:775-781, 1996). Whichever approach is used, estimates of the range and distribution of occupational exposures will be necessary to characterize the potential for adverse effects.

Dermal absorption. Estimated dermal absorption in the RCD is dependent exclusively on the results of the Belasco et al. (1981) study in rats. Also briefly discussed in the draft RCD is a benomyl dermal absorption study in humans which was used by U.S. EPA in their special review of benomyl (Jegier, 1964). The Belasco results are used in the draft RCD in preference over U.S. EPA's approach because the draft RCD assumes a longer contact rate and total body exposure. However, since the draft RCD assumes a 10% absorption rate, it is not clear how the results compare with U.S. EPA's estimate for benomyl dermal uptake. Since U.S. EPA's results are based on humans and not on rats, it is also not clear why the Belasco study in rats was used in preference to a human study. We recommend providing scientific justification for the approach used in the draft RCD.

Variability of exposure. Only average occupational exposures are addressed in the draft RCD. No discussion of the range and distribution of exposures is given. The draft document states on page 54 that this is due to the use of the Pesticide Handlers Exposure Database for estimating exposures. Output from the Pesticide Handlers Exposure Database gives 95% confidence limits on the mean. The draft RCD also states that these confidence intervals "may not represent an accurate expression of their (exposure rate) variability" (appendix A, page nine). However, there is no accompanying discussion justifying this assumption. We believe that the variability within each of the experiments in PHED provides adequate information to estimate a typical variability for occupational exposures. We recommend that the draft RCD be revised to include a quantitative estimate of the variability of exposure, including upper-bound estimates.

Discussion of Uncertainty. As in previous exposure assessments for active ingredients, the draft exposure assessment for benomyl contains a section on appraising the factors influencing exposure assessment (pages 16-18). This section states that several factors used to estimate exposure are "conservative (tend to overestimate the value of concern)." The conclusion in this section states that "These factors are operating in the occupational exposure assessment for benomyl and as they are multiplicative, the result is significant overestimates of Absorbed Daily Dosage for the various work tasks. The maximally exposed individual is adequately represented by mean estimates of exposure when all of the 'hidden' conservatism built into estimates of exposure via the dermal route are considered." The text provides four examples of assumptions

that are predicted to overestimate exposures. There is no discussion of the assumptions used in the assessment that might underestimate the exposure levels. Secondly, while difficult to do, no attempt was made to quantify the level of uncertainty for any of the factors. This section, taken as a whole, results in an emphasis on the potential overestimation, but is not balanced by a discussion of the potential underestimation.

The presentation of scientific support for the assumptions and concepts presented in this section is minimal and not quantifiable. As a result, this section describing uncertainty, which is an important component of a risk characterization, is not supported with a scientific analysis of the existing data and data gaps and may bias the reader into believing only one perspective. We recommend that this section be deleted from the draft exposure assessment and that a more inclusive and scientifically neutral discussion of uncertainty for the exposure and risk assessment be included in the main RCD where uncertainty is discussed (page 51).

Appendix C: Commodity Residue Values

This appendix appears to be incomplete, as it ends mid-sentence on page six. DPR staff informed us that this was not a mistake and that the appendix is a copy of a portion of another document. Therefore, we have apparently received the complete appendix. We recommend that the appendix be modified to avoid confusion.

Women of childbearing years and pregnant women are included in the dietary exposure analysis, and women of 20+ years are apparently included in the dietary plus occupational combined analysis. Since the major acute toxicity endpoint of concern is developmental toxicity, and other adverse effects of benomyl include teratogenicity and reproductive toxicity, these individuals when employed as mixers and loaders, applicators, and field workers represent a potentially sensitive subpopulation. This risk assessment should specifically address potential risks from dietary, occupational, and combination exposure to benomyl for both groups of potentially sensitive subpopulations.

SPECIFIC COMMENTS

Main Risk Characterization Text

Page 1. Under "Acute Toxicity," the four-hour median lethal atmospheric concentration of benomyl is presumably 2 mg/L or 2 g/m³, not 2 g/L, since the limit test concentration for particle studies is 5 mg/L.

Pages 7 to 9, "Environmental Fate." In the draft RCD, methyl 2-benzimidazolecarbamate is stated to be "... the principal degradation product...." However, the volatile toxicant butyl isocyanate

(BIC) is formed as a breakdown product in equimolar quantities with methyl 2-benzimidazolecarbamate. Therefore, it is important that both degradation products be evaluated. At the very least, the rate of formation and release of BIC after field use should be discussed here. The reference list does not include "McNally, 1990b" cited on page nine. In addition, it is not clear how it was determined that "the half-life of benomyl degrading to MBC was 3 days," because the references which were identifiable appear to have assayed pesticide residues as *combined* benomyl and MBC (see the exposure assessment, page 13); this should be clarified. Other references to the rates of degradation which may be of value to the discussion include: Calmon and Sayag, J. Agric. Food Chem. 24:311-314 and 314-317, 1976; Chiba and Veres, J. Agric. Food Chem. 29:588-590, 1981; Li and Nelson, Bull. Environ. Contam. Toxicol. 34:533-540, 1985; Monico-Pifarre and Xirau-Vayreda, JAOAC 73:553-556, 1990; Zweig et al., J. Agric. Food Chem. 31:1109-1113, 1983.

Pages 10 and 11. Dermal exposure appears to have been estimated from urinary excretion of total benomyl-derived products in 10 hours in a rat study. If so, it is not clear how this corresponds to the time course of exposure and elimination of a dermal dose in humans, particularly because of the lag time after dermal absorption before the chemical is metabolized and excreted. The urinary elimination half-life after intravenous administration in the cited rat experiment is relevant data, but it is not clear whether the half-lives cited refer to plasma $t_{1/2}$ or urinary excretion $t_{1/2}$. The dermal absorption value used in the exposure assessment (10%) appears to be a more valid approximation of total dermal exposure than the maximum value mentioned here (3.5%), although this cannot be determined from the data provided. The evaluation is hindered by the statements "After 4 hours of dermal exposure, the amount absorbed was..." and "After 10 hours of dermal exposure the amount absorbed was..." because, according to the experimental description provided, the values actually refer to the amount excreted, not absorbed. This should be clarified, and corrected as appropriate.

Page 12. The draft RCD states that "None of the dermal irritation nor sensitization studies were acceptable to DPR under FIFRA guidelines." This appears to represent data gaps in the acute toxicity information for benomyl. Summaries of the available studies were not included in the draft RCD and therefore there is not enough information to determine exactly why the studies were unacceptable to DPR and whether the data indicate acute toxicity concerns for human exposure. The draft RCD should be revised to include a summary of the available data as well as a discussion of the impact the missing or "unacceptable" data would have on the risk characterization. It is also not clear how appropriate labels, use instructions, or mitigation measures could be developed without these data for acute toxicity. The discussion should also address these issues.

Page 13 and reference section. The Carter and Laskey study is dated 1982 in the draft RCD but 1972 in the summary of toxicology data (page nine). This error should be corrected. In addition,

the Goldman et al. study is not summarized in the summary of toxicology data. For this study, the RCD should provide the dose level at which FSH was elevated.

Page 14. For the Carter et al. (1984) study the dose levels associated with the reduced sperm counts and the increased diffuse hypospermatogenesis should be specified in the RCD (this information cannot be obtained from the summary of toxicology data). There is an apparent contradiction between the draft RCD and the summary of toxicology data for the description of Dashiell (1978). The draft RCD states there was no significant effect on testicular weight and the summary of toxicity data states there was a reduction. These limitations and contradictions deserve clarification, and if in error, a correction made. The Hess et al. (1991) study that is summarized in the draft RCD is not summarized in the summary of toxicity data; we recommend that the summary of toxicity data document be revised to include this study.

Page 27. The summary paragraph for reproductive toxicity states that the parental female NOEL is 234 mg/kg-day, whereas it is stated as 210 mg/kg-day in the summary of the study at the bottom of the page. In the third paragraph under "Dietary – Rat," third line, doses are stated as gm/kg-day rather than mg/kg-day. These apparent errors should be corrected.

Page 38. The first paragraph states that MBC "is the principal product of toxicological concern." This statement has not yet been substantiated, since the toxicity of BIC has not been discussed. Radice et al. (Toxicology 123:135-142, 1997), which is not referenced in this RCD, discuss the comparative toxicity of MBC and BIC in vitro, concluding that "benomyl activity on some cytochrome P450 isoenzymes is the result of a balance between the action of the single metabolites" (MBC and BIC). Helmann and Laryea (Toxicology 61:161-169, 1990) conclude that the toxicological effects of benomyl cannot be accounted for solely by effects of MBC, except on the testis. The apparent presumption that BIC is not toxicologically relevant should be supported with appropriate citations and discussion.

Page 38. In the third paragraph, regarding hepatotoxicity of a single dose of benomyl, reference to a study on the effects of a single dose on liver enzymes without apparent hepatotoxicity may be relevant (Dalvi, Toxicology 71:63-68, 1992).

Page 41. The exposure assessment assumes 30-day/year exposures for all tasks instead of the specific number of days for each occupational exposure used in the exposure assessment prepared by the Worker Health and Safety Branch. The rationale for these differences should be discussed.

Page 43. For dietary exposure assessments, benomyl residue levels exceeding tolerance values, if any, appear to have been arbitrarily excluded from the evaluation. We recommend that all values found be included in the exposure calculations.

Page 51 (draft RCD) and page 18 (appendix A). The draft RCD suggests that the toxic effects of benomyl are highly dependent on plasma levels and that dermal exposures experienced by humans which lead to lower plasma levels would be less hazardous to experimental animals than oral exposures (of the same absorbed dose) which result in higher peak plasma levels. This is not necessarily true, in that it presumes knowledge of the mechanism(s) of action of benomyl. It is not clear, for example, how sensitive the carcinogenic effects would be to peak plasma blood level. The statements in the RCD should discuss the influence of peak blood levels only on identified toxic effects and mechanisms that are demonstrated to depend on peak blood levels. In addition, the presumption as stated in the third paragraph that the pattern of blood levels after dietary exposure in humans would more closely approximate dietary exposures in the rat than gavage exposures depends on the human consumption pattern. The draft RCD assumes for acute dietary exposures that only one food is likely to contain a high level of a chemical on any particular day. It is likely that this one food would be eaten at a single meal rather than smaller amounts during multiple meals as would be the case for feed consumption in the rat dietary exposures. We conclude that acute dietary exposures in humans are more like a gavage than dietary exposures in rats. We recommend that the discussion be modified to be more consistent with the dietary consumption patterns of humans rather than rats.

Page 54, first paragraph. We believe as discussed above that it is possible to infer a typical variability among occupational exposures from the PHED database, which should be discussed here. However, the statement that the average value represents the exposure of 50% of the workers should also be modified. Assuming a normal distribution, half the workers would have exposures equal to *or lower than* the average, while half would have exposures equal to or greater than the average. It would be appropriate to discuss the fact that exposures are often log-normally distributed, so that a few workers may have very high exposures.

Page 55, top line and first full paragraph. It is stated that the dietary exposure calculations assume exposure to "the maximum residue levels." This should be revised to state "the residue at the tolerance levels." This is because values obtained over the tolerance are discounted in the draft RCD for dietary exposure calculations and therefore the maximum residues are not used.

Appendix A, Exposure Assessment Prepared by the Worker Health and Safety Branch

Page 5. The first paragraph under "Dermal Absorption" states exposure values in $\mu\text{g}/\text{cm}^2$ of active ingredient which conflict with the doses mentioned. This appears to be because a 50% formulation was used, and the values actually refer to the formulation, not the active ingredient. In the next paragraph, the cited reference, U.S. EPA 1979, is not included in the list of references. These problems should be corrected. In the last paragraph, the discussion of the effects of butyl isocyanate as an enzyme inhibitor could be improved by referring to effects on more physiologically relevant enzymes and tissues (Dive et al., *Biochem. Pharmacol.* 36:3731-3738,

Gary T. Patterson, Ph.D., Chief
January 19, 1999
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1987; Kucera et al., *J. Environ. Sci. Health B* 30:779-799, 1995; Pauluhn and Eben, *Arch. Toxicol.* 66:118-125, 1992; Pauluhn et al., *Exp. Pathol.* 40:197-202, 1990; Radice et al., *Toxicology* 123:135-142, 1997; Staub et al., *Chem. Res. Toxicol.* 11:535-543, 1998).

Page 6. In the first paragraph, the descriptions of studies on benomyl disposition are vague. Rather than saying that the impression that rapid conversion of benomyl to MBC "may be due to a laboratory artifact," the applicable studies and the conversion rates should be discussed at length. Rate of production and release of BIC formed in the conversion of benomyl to MBC is one of the critical unresolved issues of this exposure assessment and the RCD as a whole. It would also be useful to discuss how an assay method which involves converting benomyl to MBC and assaying the total (as stated on pages 13 to 15) can distinguish between benomyl and MBC to support the statements here about benomyl half-life. For example, there might be an initial selective extraction.

Page 11. To the extent that BIC can be present in the initial formulated mixture and released into the air during application, it would be useful to discuss how effective the worker exposure mitigation strategies would be in protecting against BIC exposure. More information is required on rate of formation and potential concentration of BIC at this stage to support any estimates on worker exposures to BIC (and to MBC).

Page 18. It is not clear why the discussion of "the effect" of benomyl is considered to be "highly dependent on plasma level," considering that several toxic effects are relevant, and the mechanism of action was not discussed for any of them. We suggest that the evidence supporting this statement be supplied. The conclusion that "The maximally exposed individual is adequately represented by mean estimates of exposure when all the "hidden" conservatism built into estimates of exposure via the dermal route are considered" has not been supported by the data provided. Rather than using "hidden" conservatism, it would be better if the exposure assessment provided a straightforward discussion of the exposure parameters and their variability.



Winston H. Hickox
Secretary for
Environmental
Protection

Department of Pesticide Regulation

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Gray Davis
Governor

MEMORANDUM

TO: Gary Patterson, Supervising Toxicologist
Medical Toxicology Branch
Department of Pesticide Regulation

VIA: Keith Pfeifer, Senior Toxicologist
Health Assessment Group
Medical Toxicology Branch

FROM: Roger Cochran, Staff Toxicologist
Health Assessment Group
Medical Toxicology Branch

DATE: MAY 7, 1999

SUBJECT: RESPONSE TO OEHHA'S COMMENTS ON THE
BENOMYL RCD.

General Comments

OEHHA: It is not clear from reviewing the draft RCD whether there was a complete search of the open literature to identify relevant articles on the toxicology, mechanism of action, and pharmacokinetics of benomyl and its major breakdown products. All pertinent scientific information published in the open literature, in addition to information submitted by the registrant, should be considered in preparing a risk assessment for any pesticide active ingredient. In this regard, the literature on an important public health issue concerning benomyl, the potential for benomyl to cause anophthalmia (a birth defect resulting in no eyes), should be discussed (see more detailed comment below).

DPR: DPR always attempts to conduct a complete review of the open literature for every pesticide. The epidemiological data has been inserted under Illness Reports, and discussed for the sake of completeness. As OEHHA points out later in their review of published epidemiological studies, instances of anophthalmia in humans, reported in the Press to be due to benomyl, is a non-issue because (page 7) "...epidemiological studies, which are apparently more definitive than the original report, do not support an association between anophthalmia and benomyl..." The potential for benomyl to cause terata, including anophthalmia, was addressed in the draft RCD. Such effects occur in laboratory animals at much higher dosages than the regulatory endpoint (based on developmental toxicity) which was selected for acute exposures.

California Environmental Protection Agency

OEHHA: Of major concern is the omission of a characterization of exposure and risk for the predominant breakdown product of benomyl, butyl isocyanate (BIC). Although the compound is identified in the exposure assessment (Appendix A) as a breakdown product of benomyl, neither release nor exposure to this compound are discussed or quantified despite its high toxicity (Pauluhn and Eben, Arch. Toxicol. 66: 118-125, 1992). Page five of appendix A describes this chemical as a cholinesterase inhibitor "equivalent in potency to some organophosphates." It would be more accurate to characterize BIC as a highly irritating volatile organic compound that is a potent inhibitor of several important enzymes. The time-course of release of this potential toxic air contaminant after benomyl application and the resulting levels in ambient air cannot be determined from the information provided. We recommend that the draft RCD be revised to include a complete discussion and evaluation of the health risk information available regarding exposure to BIC from the use of benomyl in California.

DPR: We thank OEHHA for pointing out this omission. The RCD has been modified, accordingly. All of the data on environmental fate and toxicological effects of *n*-butyl isocyanate incorporated into the RCD were obtained in the open literature. Even with the inclusion of a discussion of the fate and toxicity of butyl isocyanate, however, the estimated risks associated with the use of benomyl are the same as had been described in the draft RCD.

In as much as the Air Resources Board will be monitoring for air concentrations of benomyl this year, DPR has requested that ARB also include monitoring for *n*-butyl isocyanate so that actual levels will be known.

OEHHA: The draft RCD would be improved with significant editing and reorganization. For example, the document would be enhanced by modifying appendix C (see comments below for some suggestions); and including greater detail on the methods, results, and assumptions described in the exposure assessment, particularly on the use of the Pesticide Handlers Exposure Database and the TAS exposure software. The tolerance assessment section could be moved to precede the risk appraisal section. In addition, the descriptions of reproductive and developmental toxicity studies and the subchronic studies could be combined with observed reproductive and developmental toxicity to emphasize the large body of evidence for the reproductive and developmental toxicity of benomyl. The document also needs to be checked for spelling errors.

DPR: The text was run through SpellCheck. The format and style of DPR's documents have been established to address the most sensitive toxicological endpoint for the pertinent period of exposure, as determined by the Worker Health and Safety Branch of DPR.

Specific Comments

OEHHA: Breakdown products and metabolites. A toxicological profile for butyl isocyanate (BIC), the major environmental breakdown product of benomyl, is not included in this section of the draft RCD. We recommend that the draft RCD be revised to include a summary of the toxicity of BIC, including the determination of the critical dose (i.e., NOAEL or LOAEL) for risk assessment. Other breakdown products as well as metabolites (see for example the section on pharmacokinetics) should also be identified, accompanied by a brief discussion of the known toxicology of these compounds. A flow diagram showing the pathways of benomyl metabolism and breakdown in the

environment with the chemical structures of the compounds would be a good way to address this. We acknowledge the inclusion on page eight of the two formulae for benomyl and the metabolite methyl 2-benzimidazolecarbamate (MBC). This could be expanded to include the other breakdown products and metabolites.

DPR: The toxicity data on *n*-butyl isocyanate is sparse. What toxicity data are available from the published literature have now been included. The diagram of environmental breakdown products of benomyl on page 8 has been expanded to include *n*-butyl isocyanate, as well as the other known metabolites or degradation products.

OEHHA: Administered doses. Information on the actual administered dose of benomyl to laboratory animals in dietary, drinking water, or inhalation studies is missing from the summaries of many of the experimental studies described in this section. For example, the FAO (1985) study states that the NOEL for body weight loss was 150 ppm, but no calculation was provided as to the administered dose level (in mg/kg-day). Administered dose levels were also not given for Sherman (1969b), Sherman (1972b) (rats), Warheit et al. (1989), Barnes et al. (1983), Haskell (1972), and others. Comparing results for the different studies is not possible without knowledge of the administered doses and we recommend that the document be revised to provide this information to the reader.

DPR: FAO, 1985. The data were supplied second-hand by FAO, with no information on the purity of the compound, stability of the compound in the diet, etc. The only effect reported was a decrement in body weight. This was not one of the primary endpoints of concern in the RCD.

Sherman 1969b. "The study was unacceptable to DPR under FIFRA guidelines because there was no indication that a maximum tolerated dose had been reached, there were no ophthalmoscopic exams, and the stability of the test article in the feed was not validated." As there were no toxic effects to discuss, and since there was a question as to what the administered dose was, it was not estimated.

Sherman, 1972b. From the text in the draft RCD: "The NOEL for pericholangitis-cholangiohepatitis in females was 100 ppm (approximately 4.9 mg/kg-day from food consumption data)."

Warheit et al., 1989- the estimated absorbed dose has been added.

Barnes et al., 1983- the estimated absorbed dose has been added.

Haskell, 1972 Examination of the description of the study in the draft RCD clearly indicates that there is no way to accurately estimate the absorbed dosages.

OEHHA. Reproductive toxicity. The 1968 three-generation reproductive study in rats (Sherman, 1968) is a pivotal study. The U. S. Environmental Protection Agency (U. S. EPA) in 1997 based its reference dose (RfD) of 0.05 mg/kg-day on the NOEL (5 mg/kg-day) for decreased weanling weight at the next highest dose from this study. The draft RCD concludes that the study is "not acceptable under FIFRA guidelines" for risk assessment for inadequate group size and lack of feed analysis. However, Food and Agriculture Code 14022(C) states that "the Director shall consider all available scientific data" for the TAC program. From another relevant study by Barnes et al. (1983), a LOEL of 203 ppm (10 mg/kg-day?) for decreases in male reproductive parameters might be identified. However, the draft RCD selected a NOEL of 28.2 mg/kg-day

from a different study (Mebus, 1991) on testicular parameters for risk assessment. The draft RCD does not provide enough information to assess the validity of this determination. Based on the information available, we cannot determine if the justification for not using the Sherman (1968) and the Barnes et al. (1983) studies for risk assessment is sufficient. We recommend that the RCD be revised to include a detailed description of the study designs and results and a summary of U.S. EPA's determinations and conclusions. Further justification would likely be needed to support the determination that a higher NOEL from another study for comparable effects in offspring should be used instead of the lower NOEL in the Sherman (1968) study for effects on weanlings.

DPR: Unacceptability under FIFRA guidelines does not mean that DPR will not consider using the study for risk assessment. There were basically two reasons not to use the Sherman, 1968 study. (1) Decrement in weanling weight was not dose related. Weanlings at the highest dose, 25 mg/kg-d, had no decrement in weanling weight (see your own document, page 6, paragraph 3). (2) The only durations of human exposure considered for regulation were acute (1-day), chronic (1 year), and lifetime (due to oncogenicity). Reproductive toxicity studies (both Sherman, 1968 and Barnes et al., 1983) cover a shorter time frame than 1 year, and the endpoints mentioned occurred after more than a single dose.

OEHHA: Genotoxicity. The inclusion of a large number of genotoxicity studies for benomyl and MBC in the draft RCD is noted. However, the summary of the studies does not accurately describe the weight of evidence. When considering the body of evidence for genotoxicity, a better scientific approach would be to weigh the effects from all studies submitted by the registrants and those published in the peer reviewed literature, regardless of whether they are "acceptable" according to FIFRA or TSCA guidelines. We agree that the results are mostly negative for the mutagenicity of purified benomyl (95% or greater). However, the results are equivocal for the mutagenicity of benomyl of lesser purity (50%) and for the breakdown product MBC. The number of positive studies for chromosomal aberrations for purified benomyl (95% or greater) with or without metabolic activation cannot be dismissed, and these data suggest that benomyl is genotoxic. We recommend that the summary paragraph be revised to more accurately reflect the results from all studies. The final conclusion should be revised to read "Considering all of the data, the equivocal results in gene mutation testing and the positive results in chromosomal aberration tests suggest that benomyl and MBC (or an impurity that is not always present) possess some genotoxic activity."

DPR: The text of the draft RCD says this about the weight of evidence of the genotoxicity studies, "....genotoxicity test results demonstrating the potential of MBC to interact with DNA indicate a weight of evidence which is sufficient to warrant a quantitative risk assessment."

OEHHA Selection of NOEL for acute exposure. A NOEL of 10 mg/kg MBC (15 mg/kg in benomyl equivalents) for post-implantation loss observed in a developmental study in rabbits (Feussner, 1985) was selected for the estimation of acute margins of exposure in the draft RCD. This was based on the fact that there was no significant increase in the number of litters with at least one resorption in the 10 mg/kg group (low dose) versus the controls (3/14 compared to 4/16 in the controls and the low dose group, respectively). The number of resorptions, however, in the 10 mg/kg group (16/119) was significantly increased versus that observed in the controls (3/108). The draft RCD supports the conclusion that 10 mg/kg is a NOEL by stating "the best estimate of biological effects is obtained using the litter as the unit for comparison." This is not sufficient scientific justification as to why the litter is a better measure of effects than are the

number of fetal resorptions. Additionally, since there is clearly a dose-related trend in the number of resorptions, 10 mg/kg may be a LOEL rather than a NOEL. We suggest the reevaluation of the data comparing the number of resorptions per litter as a function of dose, thus incorporating both individual and litter data into the analysis. If no further justification can be provided for using litter data rather than resorption data, we recommend that 10 mg/kg be considered a LOEL and the appropriate modification made to the risk assessment.

DPR: OEHHA is correct in stating that there was not sufficient scientific justification presented as why the litter is the best measure of effects. Through an oversight, the reference for making that statement, "USEPA's Guidelines for Developmental Toxicity Risk Assessment", was left off the end of that sentence. It is the dams which are the units that are dosed with the toxin. A more complete rationale for using litters as the unit for comparison is fully discussed by USEPA in their document.

OEHHA Selection of NOEL for chronic exposure. A chronic NOEL of 15 mg/kg-day for hepatotoxicity (cirrhosis, fatty liver, increased serum liver enzymes) was identified in a two-year benomyl feeding study in dogs (Sherman, 1970). A lower NOEL of 7.4 mg/kg-day benomyl equivalents based on hepatotoxicity (pericholangitis/cholangiohepatitis) was identified in a two-year feeding study in rats (Sherman, 1972b). The latter study, however, was determined in the draft RCD to be unacceptable according to FIFRA guidelines due to lack of feed analysis and inadequate animal group size. However, the feed analysis problem appears to have been resolved (see Summary of Toxicology Data for Benomyl, 10/1/97). Furthermore, although the group size was 36 animals/dose, numbers that might not meet FIFRA guidelines, the size of the study should be adequate for risk assessment purposes since toxicity was observed.

Based on the available data and the severity of the adverse liver effects found in several studies, we recommend that the chronic NOEL for use in the risk assessment for benomyl be 7.4 mg/kg-day and not 15 mg/kg-day as used in the draft RCD.

DPR: The lowest NOEL for repetitive exposure to MBC was in a combined chronic toxicity/oncogenicity study in the rat (Sherman, 1972b). The NOEL in benomyl equivalents was 4.9 mg MBC/kg-day x 1.5, or 7.4 mg benomyl/kg-day, with a LOEL of 37.5 mg benomyl/kg-day. However, it's important to take the entire database into consideration, rather than simply selecting the lowest NOEL as the regulatory endpoint.

The factors considered in the selection of the critical NOEL were 1) the effect of duration of exposure on hepatotoxicity of benomyl, 2) whether there were species differences in sensitivity, and 3) the effect of dose selection on the magnitude of the NOEL. In both the rat and the dog, the dose at which hepatotoxicity was manifested at 90 days (Igbedioh and Akinyele, 1992; Sherman, 1968a) was essentially the same as the LOELs for chronic exposure in the respective laboratory animals. Thus, increasing the duration of the dosing regime did not seem to affect the level at which hepatotoxicity occurred. The LOEL in one chronic dog study (20.2 mg/kg-day in benomyl equivalents) was only about half as great as the 2-year LOEL (37.5 mg benomyl/kg-day) in the chronic rat study. This indicated that the dog was at least as sensitive to benomyl as the rat with regards to hepatotoxicity. Indeed, the NOEL for hepatotoxicity in that chronic dog study (4 mg benomyl equivalents/kg-day; Sherman, 1972a) was less than the chronic rat NOEL (7.4 mg benomyl/kg-day; Sherman, 1972b). Thus, the NOELs in each of the studies were functions of dose selection. The highest NOEL (in benomyl equivalents) below the lowest LOEL (in benomyl equivalents) for hepatotoxicity in either species was 15 mg/kg-d.

Consequently, the critical NOEL, 15 mg benomyl/kg-day, used to assess margins of exposure for potential annual exposure to benomyl came from the acceptable dog study (Sherman, 1970).

OEHHA: As mentioned above, and on page 39 of the draft RCD, U.S. EPA identified a NOEL of 5 mg/kg-day based on decreased weanling weights from a three-generation rat reproduction study (Sherman, 1968). The draft RCD selected a NOEL based on hepatotoxicity from a different study that is three times higher (and therefore less health-protective) than U.S. EPA's NOEL. The rationale stated in the document is that the "study [from which U. S. EPA selected its NOEL] was not acceptable to DPR under FIFRA guidelines because of inadequate group size and lack of feed analysis despite demonstrable instability of the test article." Although there might be a regulatory basis for disregarding these data, the disagreement with U.S. EPA's selected NOEL needs further explanation and justification in the risk assessment. We reviewed the basis for the selection of the NOEL of 5 mg/kg-day by U. S. EPA and conclude that the use of this NOEL for risk assessment is not fully justified by the data (there was no effect on weanling weights at the highest dose; no dose-response was established). A comparable scientific explanation should be included in this section of the RCD to support the selection of an alternative NOEL.

We also recommend that a scientific explanation for deviation from U.S. EPA's NOEL be included in the revised RCD.

DPR: DPR's reasons for not using the Sherman, 1968 study were stated in the text of the draft RCD. (1) Decrement in weanling weight was not dose related. Weanlings at the highest dose, 25 mg/kg-d, had no decrement in weanling weight. (2) Reproductive toxicity studies cover a shorter time frame than 1 year, and there were an adequate number of chronic toxicity studies on which to base the assessment of risk for annual exposure to benomyl.

OEHHA Oncogenicity. Based on the summary information provided in the draft RCD, we agree that the Wiechman (1982) study is more appropriate for use in risk assessment than the Wood (1982) study used by U. S. EPA as the basis for the quantification of benomyl's carcinogenic potency. An additional factor supporting the use of Wiechman (1982) is that the study was conducted with benomyl instead of MBC, which was used in the study by Wood (1982). However, insufficient information was given to verify the accuracy of the human cancer potency factor derived in the draft RCD. The text states that the animal potency (which was verified using the mstage model), derived from the data using Global 86 was scaled using the factor: (body weight)^{3/4}. The animal and human body weights used in the draft RCD to perform this calculation were not presented in the text (OEHHA assumes that 70 kg and 0.03 kg were used for human and mouse, respectively). The default body weight values should be provided in the revised RCD so that the calculations can be reproduced.

DPR: The text has been modified to include the default values.

OEHHA: Epidemiological data. Available information on benomyl exposures and potential eye malformations was not discussed in the RCD. This subject was introduced into the literature by a report on clusters of anophthalmia and microphthalmia (microscopic eyes and blindness) in the UK that was associated with exposure to benomyl. Benomyl was considered a suspect chemical because of its similar effects in animal studies. This attracted public attention and concern that culminated in a lawsuit in Florida over microphthalmia in a child born to a woman who reported exposure to Benlate in the first trimester. The verdict found the pesticide manufacturer liable for

damages. However, several epidemiological studies, which are apparently more definitive than the original report, do not support an association between anophthalmia and benomyl (see, for instance, *Reprod. Toxicol.* 8:397-403, 1994; *Brit. Med. J.* 308:205, 1994; *Brit. Med. J.* 308:205-206, 1994). This topic should be discussed in the benomyl RCD to acknowledge such concerns as expressed in the article by A. Watterson, "Pesticide reproductive health hazards in humans and public health policy options: some unanswered questions and undocumented answers arising from the benomyl debate," in *J. Public Health Med.* 16:141 -144, 1994.

DPR: The epidemiological data has been inserted under Illness Reports, and discussed for the sake of completeness.

OEHHA: Inclusion of 2-[methoxycarbonylamino]-benzimidazole (MBC). MBC, one of the primary metabolites of benomyl, is assumed to be responsible for the majority of toxic effects observed following benomyl exposure. Toxicity data on MBC, after molecular weight adjustment, are considered in the draft RCD to be applicable to the assessment of benomyl risks (see page 38 for example). The draft RCD only considers benomyl and MBC derived from benomyl use in the exposure assessment. This would be appropriate if MBC was exclusively a byproduct of the metabolism of benomyl. However, there are other occupational and dietary sources of MBC. For example, thiophanate-methyl, another fungicide, is degraded and metabolized to MBC. MBC, although no longer registered for use in California, is manufactured and used as a fungicide known as carbendazim. MBC residues from the use of MBC may also contribute to the "benomyl/MBC" dietary exposure. Likewise, MBC residues from the use of compounds such as thiophanate-methyl may contribute to both the dietary and occupational "benomyl/MBC" exposures. These potential sources should be discussed and if possible quantified in the exposure assessment (e.g., appendix A) and incorporated into the assessment of margins of safety. If this is not possible due to inadequate data, a discussion on uncertainty should include the degree to which this omission would underestimate risks.

DPR: Although thiophanate methyl does form MBC as a breakdown product in the environment, or as a metabolite in mammalian systems, DPR's policy is to conduct risk assessments for the individual active ingredient and its metabolites. Thiophanate methyl does not contribute substantially to the cumulative exposure of workers or the public to MBC. Thiophanate methyl can only be used on one commodity (onions) that benomyl cannot be used on as well. In those instances where there is a label approved use on a commodity for both fungicides, either one or the other are applied. For example, although the greatest uses of benomyl and thiophanate methyl are on almonds, the two active ingredients are not used in combination or in sequence. Rather, it is one or the other active ingredient which is used, generally based on which fungicide is less costly.

When the risk assessment for thiophanate methyl is done, the dietary assessment will address carbendazim from all potential sources.

OEHHA: Inclusion of other structurally similar fungicides in the exposure assessment. To complete the risk characterization, a discussion regarding any oncogenic potential from other benzimidazole compounds would be useful.

DPR: DPR's policy calls for the RCD's to address the toxicity and exposure of the specific parent compound and metabolites and/or degradates that have potential toxicity, based on approved label uses under FIFRA.

OEHHA: Dietary exposure estimates. Dietary exposure analyses were conducted using Exposure-1 and Exposure-4 software. Little detail regarding the assumptions in using this software was provided in the text of the draft RCD and we recommend including a more detailed explanation of the assumptions used.

DPR: The information in the draft RCD should be sufficient to provide an overview of the Ex-1 and Ex4 programs. Several papers have been published by DPR personnel and Technical Assessment Systems personnel detailing the assumptions inherent in the computerized programs. OEHHA may request this information if they deem it necessary.

OEHHA: Combined Occupational and Dietary Exposure. It is not clear why the population subgroup, women 20+ years of age, was chosen to estimate the combined exposure. The rationale provided in the draft RCD is that occupational exposures were derived from agricultural workers for this subpopulation. The text suggests, however, that all of the occupational exposures were estimated for men, with the exception of field workers. The legend of Table 15 (which gives the combined exposures) also states a body weight of 75.9 kg was assumed for all work tasks by field workers and home gardeners (the activities associated with the greatest exposure). This is the body weight used in the draft RCD for men, not women. This apparent discrepancy needs to be clarified.

DPR: The text has been modified to clarify this point.

OEHHA: Margins of exposure. MOE calculations for several scenarios were checked and found to be mathematically correct. As calculated in the draft RCD based on the draft assumptions, exposure estimates, and interpretation of the data, all acute MOEs are greater than 100, a level stated in the draft RCD as being "the value conventionally recommended to protect people from the toxic effects of a chemical." However, some MOEs are relatively small (e.g., 200 to 300). If the acute NOEL of 10 mg/kg MBC (15 mg/kg in benomyl equivalents) for post-implantation loss observed in a developmental study in rabbits was selected as a LOEL rather than a NOEL as we recommend, these MOEs would be 10-fold lower, or less than 100. In addition, changes in some of the assumptions and approaches used in the exposure assessment could further decrease the MOEs. The same concerns could apply to the chronic MOEs although they are significantly higher (all are 3,000 or greater) and the resultant impact would not be as significant for public health protection. We recommend that a quantitative discussion of the uncertainties in conducting the risk assessment for noncancer endpoints be included in the revised RCD. This would include a quantification of the impact of using upper-bound rather than average exposure calculations in the exposure assessment.

DPR: An extensive discussion of the uncertainties with regards to the toxicology and the assessment of exposure is included in the Risk Appraisal. The reasons for using litters as the unit for comparison in developmental toxicity studies are based on the information presented by USEPA in their document, Guidelines for Developmental Toxicity Risk Assessment.

OEHHA: Cancer risks. Risk calculations for several scenarios were checked and found to be mathematically correct. Most of the estimated cancer risks exceed 1×10^{-6} , several do so by an order of magnitude (e.g., 14×10^{-6} for wine grape field workers). As for the noncancer effects assessment, we recommend that a quantitative discussion of the uncertainties in conducting the cancer risk assessment for benomyl be included in the revised RCD.

DPR: It has been the policy of DPR to present a range of oncogenic risk based on the animal data and the most appropriate model. Generally this range is the Maximum Likelihood Estimate to the 95th upper bound percentile. The uncertainties inherent to these probability estimates are presented and discussed in the Risk Appraisal section.

OEHHA: Federal Food Quality Protection Act. The requirement of the FQPA to account for potential pre and post-natal developmental toxicity and the completeness of the database with respect to exposure and toxicity to infants and children was discussed in the draft RCD. The document further points out that the regulatory endpoint used in the RCD for calculating MOEs for daily exposure is based on a developmental endpoint. No decision is made, however, with regard to whether an additional safety factor/margin of safety needs to be considered for the protection of infants and children from toxicity due to benomyl exposure. This is a science-based decision and should be resolved in the risk assessment. We determine from the data reviewed in the draft RCD that based on the FQPA criteria, an additional 10-fold uncertainty factor would be justified.

DPR: The issue was discussed in the text of the draft RCD, and mentioned in the Conclusions. It was recommended that an additional uncertainty factor be considered.

*OEHHA: Potential endocrine effects (mechanism of action of female reproductive effects) and cumulative and aggregate exposure (degree of underestimation by not including aggregate or cumulative exposures) need to be addressed in greater detail in this section of the RCD. In addition, other relevant studies on developmental effects of benomyl should be discussed (Ellis et al., *Teratog. Carcinog. Mutagen* 7:357-375, 1998, Ellis et al., *Teratog. Carcinog. Mutagen* 8:377-391, 1988; Hoogenboom et al., *Curr. Eye Res.* 10:601-612, 1991; Kavlock et al., *Toxicol. Appl. Pharmacol.* 62:44-54, 1982; Sherman et al., *Toxicol. Appl. Pharmacol.* 32:305-315, 1975; Zeman et al., *J. Toxicol. Environ. Health* 17:405-417, 1986).*

DPR: There is no evidence of any direct effects on the endocrine systems by benomyl or MBC. All of the actions of benomyl with regards to effects on male reproduction (sloughing of the germinal epithelium) and developmental toxicity (post-implantation loss, developmental anomalies, and terata) can be ascribed to the ability of benomyl to cause disruption of tubulin assembly and the resultant effect on cell-cell interactions and movements.

The Kavlock *et al.*, 1982 study was discussed in the draft RCD on page 36.

The Sherman *et al.*, 1975 paper is a published compilation of various FIFRA studies submitted earlier by the registrant. Those studies were discussed individually in the draft RCD.

Zeman *et al.*, 1986; Hoogenboom *et al.*, 1991; and Ellis *et al.*, 1987 discussed the effects of protein deprivation on the manifestation of benomyl's developmental toxicity in rats. At low doses of benomyl (31.2 mg/kg-day) protein deprivation tended to ameliorate the developmental toxicity of benomyl. At high doses of benomyl, 62.6 mg/kg-day and greater, protein deprivation tended to exacerbate the anomalies. Thus, the results were somewhat paradoxical. None of the studies described developmentally toxic effects of benomyl that had not been indicated already in the 13 developmental toxicity studies discussed in the draft RCD. However, for the sake of completeness the studies were included in the developmental toxicity section of the RCD.

Ellis *et al.*, 1988 examined the relationship of periventricular overgrowth to hydrocephalus in the brains of fetal rats exposed to a single dose level (62.5 mg/kg-day) of benomyl. The study suggested several theoretical mechanisms by which these specific effects of benomyl might be manifested. For the sake of completeness, this study was added to the risk assessment.

OEHHA: It is not clear how the tolerance assessment was performed. For example, a range of MOEs for several commodities is presented for "each population subgroup." Population subgroups are not defined in this section however. It should be clarified as to whether these are the same population subgroups used for the dietary assessment presented earlier in the document. We note that MOEs were less than 100 for several commodities including apples, grapes, oranges, pears, peaches, and pineapples.

DPR: DPR believes that the explanation of how the tolerance assessment was performed is sufficient. As the same computerized program (EX-4) performs the tolerance assessment and the dietary risk assessment (see text), the population subgroups are the same. DPR also noted (in the text of the draft RCD, p. 61) that the MOEs were less than 100 for specific commodities.

OEHHA Women of childbearing years and pregnant women are included in the dietary exposure analysis, and women of 20+ years are apparently included in the dietary plus occupational combined analysis. Since the major acute toxicity endpoint of concern is developmental toxicity, and other adverse effects of benomyl include teratogenicity and reproductive toxicity, these individuals when employed as mixers and loaders, applicators, and field workers represent a potentially sensitive subpopulation. This risk assessment should specifically address potential risks from dietary, occupational, and combination exposure to benomyl for both groups of potentially sensitive subpopulations.

DPR: The draft RCD does specifically address the potential risks from dietary, occupational, and combined exposure to benomyl for women of childbearing years..

OEHHA: Under "Acute Toxicity," the four-hour median lethal atmospheric concentration of benomyl is presumably 2 mg/L or 2 g/m³, not 2 g/L, since the limit test concentration for particle studies is 5 mg/L.

DPR: The problem in the table has been corrected.

*OEHHA: "Environmental Fate." In the draft RCD, methyl 2-benzimidazolecarbamate is stated to be "... the principal degradation product...." However, the volatile toxicant butyl isocyanate (BIC) is formed as a breakdown product in equimolar quantities with methyl 2-benzimidazolecarbamate. Therefore, it is important that both degradation products be evaluated. At the very least, the rate of formation and release of BIC after field use should be discussed here. The reference list does not include "McNally, 1990b" cited on page nine. In addition, it is not clear how it was determined that "the half-life of benomyl degrading to MBC was 3 days," because the references which were identifiable appear to have assayed pesticide residues as combined benomyl and MBC (see the exposure assessment, page 13); this should be clarified. Other references to the rates of degradation which may be of value to the discussion include: Calmon and Sayag, J. Agric. Food Chem. 24:311-314 and 314-317, 1976; Chiba and Veres, J. Agric. Food Chem. 29:588-590, 1981; Li and Nelson, Bull. Environ. Contam. Toxicol. 34:533-540, 1985; Monico-Pifarre and Xirau-Vayreda, JAOAC 73:553-556, 1990; Zweig *et al.*, J. Agric. Food Chem. 31:1109-1113, 1983.*

DPR: As stated above, the available information from the published literature on the evolution and environmental fate of *n*-butyl isocyanate has been incorporated into the RCD. The reference McNally, 1990b was in the reference section, however there was no "b" after the year 1990. This has been corrected.

OEHHA: Dermal exposure appears to have been estimated from urinary excretion of total benomyl-derived products in 10 hours in a rat study. If so, it is not clear how this corresponds to the time course of exposure and elimination of a dermal dose in humans, particularly because of the lag time after dermal absorption before the chemical is metabolized and excreted. The urinary elimination half-life after intravenous administration in the cited rat experiment is relevant data, but it is not clear whether the half-lives cited refer to plasma $t_{1/2}$ or urinary excretion $t_{1/2}$. The dermal absorption value used in the exposure assessment (10%) appears to be a more valid approximation of total dermal exposure than the maximum value mentioned here (3.5%), although this cannot be determined from the data provided. The evaluation is hindered by the statements "After 4 hours of dermal exposure, the amount absorbed was. ..." and "After 10 hours of dermal exposure the amount absorbed was..." because, according to the experimental description provided, the values actually refer to the amount excreted, not absorbed. This should be clarified, and corrected as appropriate.

DPR: As was noted in the text, the amount of benomyl absorbed through the skin varied. The factors influencing absorption were (1) the amount applied [a greater percentage of less concentrated solutions are absorbed], and (2) the duration of exposure [longer exposures result in a higher percentage of absorption]. As 95% of an *iv* administered dose came out in the urine, it is reasonable to assume that the amounts recovered from the urine effectively indicate the absorbed dose.

OEHHA: The draft RCD states that "None of the dermal irritation nor sensitization studies were acceptable to DPR under FIFRA guidelines." This appears to represent data gaps in the acute toxicity information for benomyl. Summaries of the available studies were not included in the draft RCD and therefore there is not enough information to determine exactly why the studies were unacceptable to DPR and whether the data indicate acute toxicity concerns for human exposure. The draft RCD should be revised to include a summary of the available data as well as a discussion of the impact the missing or "unacceptable" data would have on the risk characterization. It is also not clear how appropriate labels, use instructions, or mitigation measures could be developed without these data for acute toxicity. The discussion should also address these issues.

DPR: Neither dermal irritation studies, nor dermal sensitization studies are covered by SB950 requirements, so the lack of FIFRA acceptable studies are not considered data gaps under SB950. As USEPA sets data requirements for labels, such "data gaps" fall under their jurisdiction.

OEHHA: The Carter and Laskey study is dated 1982 in the draft RCD but 1972 in the summary of toxicology data (page nine). This error should be corrected. In addition, the Goldman et al. study is not summarized in the summary of toxicology data. For this study, the RCD should provide the dose level at which FSH was elevated.

DPR: The text has been revised appropriately.

OEHHA: For the Carter et al. (1984) study the dose levels associated with the reduced sperm counts and the increased diffuse hypospermatogenesis should be specified in the RCD (this information cannot be obtained from the summary of toxicology data). There is an apparent contradiction between the draft RCD and the summary of toxicology data for the description of Dashiell (1978). The draft RCD states there was no significant effect on testicular weight and the summary of toxicity data states there was a reduction. These limitations and contradictions deserve clarification, and if in error, a correction made. The Hess et al. (1991) study that is summarized in the draft RCD is not summarized in the summary of toxicity data, we recommend that the summary of toxicity data document be revised to include this study.

DPR: The errors cited have been corrected.

OEHHA: The summary paragraph for reproductive toxicity states that the parental female NOEL is 234 mg/kg-day, whereas it is stated as 210 mg/kg-day in the summary of the study at the bottom of the page. In the third paragraph under "Dietary - Rat," third line, doses are stated as gm/kg-day rather than mg/kg-day. These apparent errors should be corrected.

DPR: The errors cited have been corrected.

OEHHA: The first paragraph states that MBC "is the principal product of toxicological concern. This statement has not yet been substantiated, since the toxicity of BIC has not been discussed. Radice et al. (Toxicology 123: 135-142, 1997), which is not referenced in this RCD, discuss the comparative toxicity of MBC and BIC *in vitro*, concluding that "benomyl activity on some cytochrome P450 isoenzymes is the result of a balance between the action of the single metabolites" (MBC and BIC). Helmann and Laryea (Toxicology 61: 161-169, 1990) conclude that the toxicological effects of benomyl cannot be accounted for solely by effects of MBC, except on the testis. The apparent presumption that BIC is not toxicologically relevant should be supported with appropriate citations and discussion.

DPR: The Hellman and Laryea, 1990 paper examined the ability of benomyl and MBC to affect the *in vivo* incorporation of ³H-thymidine into several body organs in the mouse. They found that benomyl, but not MBC had this inhibitory ability. Although butyl isocyanate was mentioned in their paper, the authors did not attribute the inhibition of ³H-thymidine incorporation to butyl isocyanate.

Examination of the toxicological database for benomyl and MBC contained in the draft RCD indicates there is not much difference in the toxicological effects of the two compounds on an equimolar basis in acute, subchronic, chronic, or lifetime exposure studies in laboratory animals. If there were highly significant toxicological effects of butyl isocyanate, the results of those studies involving benomyl (which produces *n*-butyl isocyanate upon being metabolized) should be markedly different from those that utilized MBC. The fact that the results are not significantly different argues that effects of *n*-butyl isocyanate, produced by metabolism of benomyl *in vivo*, are also insignificant under actual conditions.

OEHHA: In the third paragraph, regarding hepatotoxicity of a single dose of benomyl, reference to a study on the effects of a single dose on liver enzymes without apparent hepatotoxicity may be relevant (Dalvi, Toxicology 71:63-68, 1992).

DPR: The study has been incorporated into the pharmacokinetics portion of the RCD. In as much as the study demonstrates that some aspects of liver function can be affected by a single dose of benomyl, it is a relevant piece of supplemental information.

OEHHA: For dietary exposure assessments, benomyl residue levels exceeding tolerance values, if any, appear to have been arbitrarily excluded from the evaluation. We recommend that all values found be included in the exposure calculations.

DPR: DPR does not include the illegal residue levels of pesticides when assessing dietary risk in the Risk Characterization Document. As is stated in the document, "Over-tolerance incidents are separately investigated by the DPR Pesticide Enforcement Branch. The potential risk from consuming commodities with residues over tolerance levels is evaluated by the Medical Toxicology Branch using an expedited acute risk assessment process."

OEHHA: The draft RCD suggests that the toxic effects of benomyl are highly dependent on plasma levels and that dermal exposures experienced by humans which lead to lower plasma levels would be less hazardous to experimental animals than oral exposures (of the same absorbed dose) which result in higher peak plasma levels. This is not necessarily true, in that it presumes knowledge of the mechanism(s) of action of benomyl. It is not clear, for example, how sensitive the carcinogenic effects would be to peak plasma blood level. The statements in the RCD should discuss the influence of peak blood levels only on identified toxic effects and mechanisms that are demonstrated to depend on peak blood levels. In addition, the presumption as stated in the third paragraph that the pattern of blood levels after dietary exposure in humans would more closely approximate dietary exposures in the rat than gavage exposures depends on the human consumption pattern. The draft RCD assumes for acute dietary exposures that only one food is likely to contain a high level of a chemical on any particular day. It is likely that this one food would be eaten at a single meal rather than smaller amounts during multiple meals as would be the case for feed consumption in the rat dietary exposures. We conclude that acute dietary exposures in humans are more like a gavage than dietary exposures in rats. We recommend that the discussion be modified to be more consistent with the dietary consumption patterns of humans rather than rats.

DPR: There are basically two factors to consider in an absorption evaluation when comparing the dermal versus the oral route: the time to peak concentration, and the peak concentration. These are particularly important for acute effects. The total amount absorbed (Area Under the Curve- AUC) and distribution/excretion factors become more important for longer term toxicity (Amdur, Doull, and Klassen, Eds. Casarett and Doulls Toxicology, 1991).

Dietary exposure estimates are a function of two components- residues on the food, and the amount of food consumed. Human consumption in the national surveys was reported as the amount of food consumed in a 24 hour period- not one sitting. A gavage dose is administered in a matter of seconds, contained in a solvent designed to solubilize the test agent, and generally results in maximum bioavailability. Also, with a gavage dose, there is no interaction with the foodstuff on which residues are carried in dietary exposures. For further information on the assumptions that go into the acute dietary exposure assessment see: Cochran, R.C., J. Kishiyama, C. Aldous, W.C. Carr, Jr., and K.F. Pfeifer, 1995. Chlorpyrifos: Hazard assessment based on a review of the effects of short-term and long-term exposure in animals and humans. **Food Chem. Toxicol.** 33(2):165-172. Finally, it is generally assumed that blood levels of a

toxin are representative of tissue concentrations of that same toxin under steady state conditions.

OEHHA: We believe as discussed above that it is possible to infer a typical variability among occupational exposures from the PHED database, which should be discussed here. However, the statement that the average value represents the exposure of 50% of the workers should also be modified. Assuming a normal distribution, half the workers would have exposures equal to or lower than the average, while half would have exposures equal to or greater than the average. It would be appropriate to discuss the fact that exposures are often lognormally distributed, so that a few workers may have very high exposures.

DPR: Questions on exposure assessment will be answered by WH&S.

OEHHA: It is stated that the dietary exposure calculations assume exposure to "the maximum residue levels." This should be revised to state "the residue at the tolerance levels." This is because values obtained over the tolerance are discounted in the draft RCD for dietary exposure calculations and therefore the maximum residues are not used.

DPR: The wording in the draft RCD reads: "The residue data for a dietary exposure assessment are based on DPR and federal monitoring programs, field trials, and survey studies. In the absence of data, surrogate data from the same crop group, as defined by USEPA, or USEPA tolerances are used. Residue levels that exceed established tolerances are not used in the dietary exposure assessments. Over-tolerance incidents are separately investigated by the DPR Pesticide Enforcement Branch. The potential risk from consuming commodities with residues over tolerance levels is evaluated by the Medical Toxicology Branch using an expedited acute risk assessment process."



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MEMORANDUM

TO: Dr. Anna M. Fan, Chief
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment

FROM: Charles M. Andrews, Chief
Worker Health and Safety Branch

DATE: July 28, 1999

SUBJECT: RESPONSE TO OFFICE OF ENVIRONMENTAL HEALTH HAZARD
ASSESSMENT COMMENTS ON DRAFT BENOMYL RISK
CHARACTERIZATION DOCUMENT

The Office of Environmental Health Hazard Assessment (OEHHA) completed its review of the Draft Benomyl Risk Characterization Document (RCD) on January 19, 1999. Their comments indicate there was a concern regarding the depth of the Department of Pesticide Regulation's literature search to support the positions in the RCD. In general, the assumptions and the conclusions stated in the draft were opined to need more scientific support and analysis in order to provide a complete characterization of the risks associated with the use of benomyl in California. This memorandum responds to the exposure assessment questions raised in their review.

Page 7. Aggregate Exposure from Various Sources of 2-[Methoxycarbonylamino]-Benzimidazole (MBC):

MBC is one of the primary metabolites of benomyl and is assumed to be responsible for the majority of the toxic effects related to benomyl exposure. As indicated in their memo, there are other potential sources of MBC that could increase the aggregate occupational and dietary exposure to MBC. Thiophanate-methyl, an agricultural fungicide, also has MBC as one of its primary metabolites. MBC itself is a fungicide and is known under the common chemical name as carbendazim. Although not registered in California, several products with carbendazim are registered with the U.S. EPA.

In regard to aggregate exposure to MBC, I would like to address the dietary sources first. Sources of dietary exposure to carbendazim are expected to be inadvertent. Food use tolerances for carbendazim residues in eggs, meat, poultry and wheat have been pending at U.S. EPA since 1988. A tolerance is necessary before carbendazim can be registered for use on an agronomic crop.

A review of the reported uses of benomyl and thiophanate-methyl in the Department of Pesticide Regulation (DPR) annual use reports can provide a prospective on the use of these two fungicides. In 1995, 89 percent of the reported use of benomyl was on almonds, celery, grapes, pistachios, stone fruits and strawberries. For thiophanate-methyl, 91 percent of the total use reported was on almonds, greenhouse grown plants and nursery stock, landscape maintenance

and stone fruits. There is only significant use of both chemicals reported on almonds and stone fruits. The applications of these chemicals on almonds and stone fruits are essentially bloom sprays that take place in February and March. Both chemicals have similar activity on the same spectrum of fungal diseases and similar application instructions. In general, one application is made per season at the start of bloom with a second application after 10 days if wet weather persists. Both product labels recommend applying their product in combination with a nonbenzimidazole fungicide. Normal cultural practices would dictate that a grower will apply one chemical or the other and not both during the growing season to avoid resistance development. As these applications take place several weeks to several months before harvest, the likelihood of significant MBC residues present at harvest is minimal. For a particular treated commodity, it is unlikely to carry residues of MBC from multiple sources.

A similar argument can be made for aggregate sources of MBC for occupational exposure. Because of the similarity of benomyl and thiophanate-methyl in their activity against the common bloom diseases, growers are going to use one chemical or the other. There is no advantage to applying one fungicide followed by a second spray with the other fungicide. Price, personal experience and availability will dictate which fungicide will be used for the bloom spray. The other major uses of either chemical are not in common with each other. The probability of landscape maintenance personnel and nursery-greenhouse workers also working for farmers growing celery and strawberries is unlikely. The likelihood of applicators experiencing occupational exposure to both benomyl and thiophanate methyl is not significant.

Carbendazim is registered for use as a preservative for adhesives, paints, wood, textiles for protection against microbial breakdown. These products are usually applied during the manufacturing process with minimal exposure to the applicator. Again the likelihood of these workers also applying other products that contain benomyl or thiophanate-methyl is not significant. Although a valid concern, it is unlikely that an applicator will experience aggregate exposures to MBC from applying benomyl, thiophanate-methyl or carbendazim.

Page 8 and 9. Home Use Exposure Assessment & Use of Gloves for Residential Exposure: The review comments on the surrogate study used to estimate the exposure for home gardeners applying a benomyl product. In the study, most of the participants did not wear gloves, but the assessment was conducted with the assumption that gloves should be worn when handling benomyl. The OEHHA reviewer indicates that exposure should be assessed with the applicators not wearing gloves. The exposure assessment for the home gardener was included in the RCD as an oversight. Du Pont Chemical is not producing technical benomyl that can be used to formulate consumer-use products. The Green Light Company has the only home-garden product currently registered in California that contains benomyl. They are maintaining this registration to only cover the product that may remain at retail outlets. The exposure of homeowners to benomyl from the use of a home-garden product is not an issue. The RCD needs to be amended to delete the text and references related to exposure for the home-gardener.

Page 10. Illness Reports:

A discussion of the possible relationship between occupational exposure and documented illnesses would be of value if the occurrence of these illnesses were significant. Almost 15,000 benomyl applications were reported in 1995. However, documented illnesses related to benomyl exposure are rare. As indicated in the text, only a few cases were reported per year from 1984-1993. And many of these cases are reported as exposures to benomyl mixed with other fungicides. The actual symptoms reported may be due to exposure to the other fungicides.

The study cited in the OEHHA review (Koehler and Moye) hypothesized that the level of airborne residues of chlorpyrifos present after an indoor carpet treatment were affected by the type of formulation applied. Their results indicate that formulation type, ventilation and time after treatment can have an effect on the concentrations of airborne chlorpyrifos present after a carpet treatment. However, because there are so few reported cases of over exposure to benomyl, an analysis of the circumstances surrounding each reported benomyl illnesses to appraise a cause and effect relationship would not be productive.

Most of the occupational exposure illnesses attributed to benomyl were reported as skin rashes and eye irritation. A few systemic illnesses were reported as the result of an accidental exposure due to equipment failure or ingestion of freshly treated fruit. The effects for which MOE's are estimated in the RCD appear generally unrelated to the illnesses observed in the Pesticide Illness Surveillance Program.

Page 10. Use of Pesticide Handlers Exposure Database (PHED) to Estimate Occupational Exposure:

We agree that the most desirable approach is to use good quality chemical-specific exposure data to assess occupational exposure. For benomyl, the exposure data for applicators was limited to one study. As discussed in the RCD, this study (Everhart and Holt, 1982) was limited in its scope with very short exposure replicates (1.5-5 minutes each). With such short replicates, exposure often occurs at levels that are not detectable. When this occurs, one half the minimum detectable limit (MDL) is often used as the exposure value for a dosimeter. The exposure detected from this five-minute replicate is then normalized for an eight-hour workday. Depending on the sensitivity of the analytical methods for a particular chemical, the exposure estimate can often grossly overestimate or underestimate the actual exposure. Ideally, the replicates should monitor a long enough portion of the workday (1-4 hours) to capture some exposure at detectable levels.

A second reason the study is not of good quality is because only a limited portion of the applicator's body was monitored for exposure (hands, forearms, shoulders, and face). The researchers assumed the rest of the body was protected from exposure by work clothing. Data from other exposure studies indicate that work clothing can provide various degrees of protection from pesticides. A default value of 90% protection was derived from several studies by the Worker Health and Safety Branch (HS Report 1612).

The quality control measures undertaken in the study were marginal. The sampling dosimeters were not spiked in the field to measure environmental losses. A "chain of custody" report that summarizes the collection and analysis of the samples was not provided. The laboratory methods used to analyze the samples were not validated for the percent of recovery.

Because of these problems, the results from the Everhart and Holt study (1982) was deemed to be of questionable quality and the PHED database was used to derive surrogate exposure information.

A second study by Heekstra (*et al.*, 1996) was cited in the OEHHA review as a possible source of additional exposure data. The National Institute of Occupational Safety and Health (NIOSH) conducted the study to investigate various health complaints attributed to the greenhouse use of Benlate 50 DF[®] (a dry flowable formulation of benomyl). Exposure to workers from mixing and applying benomyl or contact with residues on treated foliage was assessed with dermal dosimetry, biomonitoring and air sampling. The applications were made under a U.S. EPA experimental use only license since DuPont Chemical withdrew the ornamental registrations of benomyl in 1991. The applications were made up to a maximum of 8X the label rate with treatments made on a continuous basis for several days. In light of these extreme application conditions, the study did not monitor exposure under typical use conditions. The detected exposure would not be expected to be typical and the information is only useful for estimating upper bound values for exposure. The exposure information is not appropriate for use in the benomyl RCD.

In regard to other recommendations cited in the OEHHA review, many are beyond the scope of this document. This document is meant to be an exposure assessment for benomyl and not a comprehensive review on the methods for assessing occupational exposure.

Surrogate data can be used from exposure studies of chemicals with similar application methods and physical properties if the information is not proprietary. If either source of information is not available, then by default, the PHED database can be used to estimate exposure. This database is used also by U.S. EPA to estimate occupational exposure when chemical specific exposure information is limited or not available. And registrant's submit PHED derived exposure assessments in lieu of conducting actual studies to estimate occupational exposure. The PHED database does have its limitations for use in estimating occupational exposure, but it has the advantage of utilizing the results from many similar studies to estimate exposure.

In the PHED database, the studies are categorized on the basis of application method, work task and clothing worn which are the predominate factors that determine occupational exposure. Since most pesticides are applied with water (1-3 percent solutions), their movement in the environment during application is determined primarily by the physical characteristics of water. The physical characteristics of each pesticide (vapor pressure, solubility, etc.) are secondary in their importance for influencing exposure during application. While vapor pressure has a

significant impact on clothing penetration, very few replicates in PHED were obtained with high vapor pressure compounds.

Page 11. Dermal Absorption:

The OEHHA review indicates that a human dermal absorption study was discussed in the RCD, but the results from a rat study were used to estimate the dermal absorption rate for humans. The RCD text was interpreted to indicate that a human dermal absorption study was conducted. However, review of the U.S. EPA Benomyl Position Document 2/3 cited as the reference (U.S. EPA, 1979) indicate the rat data from the Belasco (*et al.*, 1981) study was used to estimate a human dermal absorption rate. The text in the draft RCD should be amended to clearly indicate that available dermal absorption data is from rats.

Page 11. Variability of Exposure:

The exposure estimates derived from the PHED database are expressed as mean values of exposure per pound of active ingredient (A.I.) handled. The database is composed of the results from a population of studies that do not follow a standardized protocol. And because of the great variability inherent in the data, the mean is the most stable value. The upper-end values would be unrealistically high if they were derived from the confidence limits provided for the arithmetic mean. The PHED subsets given in the Appendix of the benomyl exposure assessment indicate the 95 percent confidence limits (C.I.) for the arithmetic mean include negative values. Therefore, the use of the 95 percent C.I. from such a statistical interval is meaningless. In order to have a negative value for the mean exposure rate (even though physically impossible), the sample set must contain two clusters of exposure rates representing two extremes that are very far apart, with the lower extreme group dominating.

Arithmetic means calculated from lognormal distributions are often at the 75th percentile or thereabouts. For the type of lognormal distribution that has the lower extreme group so dominating as described above, the arithmetic mean would be at a higher percentile, like the 85th or above. The mean plus the upper 90 percent or 95 percent C.I. from this type of distribution would yield an upper extreme that is materially unreal. Although PHED cannot provide realistic upper-end values for the exposure rates, it is important to note these rates are expressed as exposure per pound of A.I. handled. If the total amount of A.I. handled per workday are maximum estimates, then the estimate of the daily exposure is likely to be overestimated even when using a mean exposure rate.

Page 14. Estimated Annual Exposure Days:

The RCD has been amended to reflect the range of estimated annual exposure days (6-60 days) depending on the work task, instead of a mean value of 30 days for all work tasks.

Page 15. Variability in PHED Data:

As discussed in the previous section, the variability in the individual studies that comprise the PHED database is not a valid concern. The user of the PHED database accepts the condition that the variability of the observations in each study is not quantified and the mean is the most stable

value produced by a PHED subset. Most exposure observations have a lognormal distribution and the mean exposure rate actually represents typically 65-75 percentile of the test population. The statement in the RCD addressing how the mean value represents the exposure of 50 percent of the test population does need to be modified. Thanks for catching that inconsistency.

Page 15. Animal Metabolism of Benomyl:

The conversion of mg of product (50% WP) to μg of A.I. per cm^2 is correct (example: $0.2 \text{ mg product} \times 0.50 \div 25.8 \text{ cm}^2 \times 1,000 \mu\text{g/mg} = 4 \mu\text{g of A.I./cm}^2$). Text has been added to indicate the dermal dose is presented as mg of product. The U.S. EPA citation has been added to the document. The Biological Disposition section has been merged with the Animal Metabolism section. As the discussion of the toxicity of metabolites is not within the scope of the exposure assessment document, the text regarding butyl isocyanate toxicity has been deleted. However, since MBC is considered by most researchers to be the actual active ingredient, the text pertaining to MBC has been retained.

Page 16. Benomyl Deposition:

The results from the benomyl deposition studies are provided as background to indicate that MBC may be relatively stable in the field. The details of each study are not necessary and can be ascertained if needed from the reference cited. The RCD is treating MBC as a stable compound when estimating the absorbed dose and no losses are assumed to occur from degradation.

The focus of concern in the benomyl exposure assessment is the primary metabolite MBC that has the potential to cause developmental toxicity in rabbits. Butyl isocyanate is only a transitory metabolite that degrades rapidly to carbon dioxide and butylamine. In water, the estimated half-life of butyl isocyanate is 14-minutes (Moye *et al.*, 1978). Data regarding the production or degradation of butyl isocyanate under field conditions are not available.

The purpose of the comments regarding the degradation of benomyl to MBC is not clear. A discussion of the assay methods is beyond the scope of the RCD. The results are summarized in the RCD and the details of the methodology can be obtained in the cited study.

Page 16. Physical & Chemical Properties of Butyl Isocyanate:

Little information is available concerning the physical and chemical properties of butyl isocyanate. The vapor pressure is 1.76×10^{-1} (Daubert and Danner, 1989). In water, butyl isocyanate rapidly hydrolyzes to butylamine and carbon dioxide (Ulrich, 1989). The half-life in water is approximately 14 minutes (Moye *et al.*, 1978). The Statement of Composition for Benlate® Fungicide does not include butyl isocyanate as a contaminant. Butyl isocyanate is a strong eye irritant that will cause a "tearing" response in humans at low concentrations. The primary reported symptom of occupational exposure to benomyl is dermal irritation. It's possible that butyl isocyanate can be produced when benomyl is mixed with water for application. But the data indicates it has a very short half-life in water (14 minutes). More information on the degradation of benomyl in water would be nice, but it is not available. I think applicator exposure to butyl isocyanate is insignificant and is not an issue.

Page 16. Toxic Effects of Benomyl:

The toxic effect of concern identified in the RCD is the ability of the major metabolite, MBC, to cause developmental toxicity in rabbits. Other adverse health effects may occur from exposure to benomyl or MBC, but their NOELs may be much greater and can only occur after a massive exposure. The purpose of the RCD is to focus on the toxic effect that is most likely to occur from doses incurred from occupational and dietary exposure. A discussion of all the possible adverse health effects, regardless of exposure level, is not relevant for the RCD.

The majority of the occupational exposure for applicators occurs via the dermal route. The inhalation route typically accounts for only 1-3 percent of the total exposure (Wolf, 1976). As the residues are absorbed, the circulatory system is the primary vehicle for moving the toxicant to the site of action. As most toxic effects have a threshold level that must be reached before the effect is manifested, the plasma level of the toxicant is the best indication for predicting the onset of the toxic affect. The plasma levels of benomyl will peak much faster and at higher levels from a massive oral dose than from a dermal dose. The skin acts like a buffer to slowly release the absorbed dose into the circulatory system.

The Branch has chosen to provide an appraisal of the various factors used in estimating occupational exposure and how the absorbed dose relates to an animal study derived NOEL. This appraisal can be used to guide the Department managers when risk management decisions regarding benomyl need to be made. It is not always possible to mitigate exposure to the level where there is an adequate margin of exposure (MOE) for a given toxic effect, particularly if the estimated exposure represents an upper-bound value. The appraisal will indicate how conservative the exposure estimates are. Again, an in-depth discussion of the variability of exposure parameters is beyond the scope of an exposure assessment.

We agree that the maximally exposed individual is not adequately represented. Exposure study protocols are not designed to quantify the upper limit of exposure from a catastrophic accident. Thus, we have revised the statement to read, "A realistic upper bound estimate of exposure under normal use conditions is adequately represented by the mean estimates of exposure when all the unacknowledged conservatism built into the estimate of exposure via the dermal route are considered".

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