UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

March 8, 2001

SUBJECT: **Benomyl:** HED Revised Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No. 099101. Barcode: D267478.

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Attached is HED's revised preliminary risk assessment of the fungicide, benomyl, for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. This assessment aggregates the risk estimates for carbendazim or methyl 2-benzimidazole carbamate (MBC), which is a common metabolite of benomyl and thiophanate-methyl. Cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity is not addressed in this document. This assessment incorporates the "error-only" comments received from the registrant during Phase I of the Tolerance Reassessment Advisory Committee (TRAC) process. This revision also incorporates data from ten pharmacokinetic studies submitted in August 2000. The disciplinary science chapters and other supporting documents for the benomyl RED are also included as attachments as follows:

Report of the Hazard Identification Assessment Review Committee. Deborah Smegal (March 2001)
Report of the FQPA Safety Factor Committee. B. Tarplee (July 1, 1999; HED Doc No. 013544)
Toxicology Chapter for Benomyl and Carbendazim. Deborah Smegal (January 31, 2001, D272363)
Occupational and Residential Exposure Assessment for Benomyl. Gary Bangs (January 31, 2001, D269486)
Summary of Potential Exposure to MBC Resulting from Residential Uses of Thiophanate-Methyl (March 8,

2001, D273295)
Acute, Chronic and Cancer Dietary Exposure to Benomyl and to the Metabolites from Benomyl - Carbendazim and 2-Aminobenzamidazole J. Morales/D. Soderberg to D. Smegal/D. Fuller. D268933, October 11, 2000.
Revised Product and Residue Chemistry Chapter. Jose Morales (February 7, 2001; D275445)
Tier 1 Estimated Environmental Concentrations for Benomyl and its major degradate, MBC. R. Pisigan 11/29/2000.
Revision in Drinking Water Assessment for Benomyl. Jon Peckenpaugh (5/4/99)
Tier 1 Estimated Environmental Concentrations for Thiophanate-methyl and its major degradate, MBC. R. Pisigan/I. Abdel-Saheb, 1/19/2001.

HED's Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicological database for benomyl and its primary metabolite, carbendazim or MBC and selected toxicological endpoints for acute, short- and intermediate-term oral, chronic oral and for short-, intermediate and long-term dermal and inhalation exposure risk assessment on June 1, 1999 and February 20, 2001 (memorandum dated March 2001). HED's FQPA Safety Factor Committee reviewed the hazard and exposure data for benomyl on June 7, 1999 and recommended that the FQPA Safety Factor (as required by Food Quality Act of August 3, 1996) of 10X be retained in assessing the risk posed by this chemical (memorandum dated July 1, 1999).

REVISED PRELIMINARY HUMAN HEALTH RISK ASSESSMENT:

BENOMYL

March 8, 2001

Health Effects Division

Office of Pesticide Programs

U.S. Environmental Protection Agency

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a Preliminary Human Health Risk Assessment for the active ingredient benomyl for the purposes of making a reregistration eligibility decision (RED). The toxicological database is adequate to support reregistration. Residue chemistry requirements are substantially complete pending receipt of limited confirmatory data. The Agency has no handler or post-application data on exposure during mixing, loading, or applying pesticides in slurry form (i.e., commercial seed/seedling treatment uses, or dip treatments), and additional data are requested to support these uses.

Benomyl [methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate], a benzimidazole carbamate, is a systemic foliar fungicide registered for control of a wide range of diseases of fruits, nuts, vegetables, and field crops. Benomyl is manufactured in the United States by E.I. du Pont de Nemours & Company (DuPont) and is sold under the trade name of Benlate®. Benomyl is formulated as a wettable powder (WP), wettable powder in water soluble packets (WSP) and in an oil dispersible (OD) powder formulation, all of which contain 50% active ingredient (a.i.). These formulations are registered for food/feed use, and may be applied as delayed dormant, foliar, seed, and seed piece treatments. Benomyl is not registered for residential use. Information from the Registrant indicates that the estimated annual usage of benomyl has declined nearly 40% since 1996 due to the cancellation of several benomyl formulated products and the registration of reduced risk fungicides.

Tolerances for residues of benomyl are currently expressed in terms of benomyl and its metabolites containing the benzimidazole moiety in/on plant, animal, and processed food/feed commodities. However, the HED Metabolism Committee recently recommended that the tolerance expression in 40 CFR §180.294(a) and (b) be modified to include residues of benomyl, carbendazim (MBC; methyl 2-benzimidazole carbamate), and 2-AB (2-amine-1-H-benzimidazole) in plant commodities, and benomyl, 5-HBC (methyl-5-hydroxybenzimidazole carbamate) and 4-HBC (methyl-4-hydroxybenzimidazole carbamate) in animal commodities. Based on the revised tolerance expression, the current enforcement and data collection methods are acceptable for all residues of concern in animal commodities. However, the current enforcement method is not acceptable for residues of concern in plant commodities because it does not detect 2-AB. All residues of concern are evaluated in this risk assessment.

There are approximately 83 tolerances for food/feed commodities such as citrus, vegetable crops, oats, rice and wheat, etc. Plant commodity tolerances range from 0.2 ppm to 50 ppm (bean vine forage). Animal commodity tolerances range from 0.1 ppm (milk, eggs, and fat, meat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep) to 0.2 ppm (liver of poultry). HED is aware of mushroom data that might support a lower tolerance on this commodity, however these data have not been formally submitted to the Agency. HED will determine the adequacy of the mushroom residue data once it has been formally submitted for review.

Benomyl is rapidly metabolized or hydrolyzed under aqueous conditions to its major metabolite carbendazim or MBC (methyl 2-benzimidazole carbamate), which is also a systemic fungicide. Hence, environmental residues are primarily as MBC, and the EPA analytical method determines benomyl residues in food as MBC (i.e., the method involves hydrolysis, so any benomyl residue would be converted to MBC prior to analysis). Consequently, this report evaluates the exposures

and risks associated with both benomyl and its major metabolites MBC and 2-AB in plants and MBC and 5-HBC and 4-HBC in animal commodities. MBC is also an environmental degradate of thiophanate-methyl, another fungicide registered for use on food and in residential settings (i.e., lawn and home orchard treatment). In addition, MBC is registered for tree injection and as a fungicide/preservative in paints, coatings, plaster and adhesives in residential settings. Consequently, residents could be exposed to MBC via dermal and inhalation exposure during painting activities, and via inhalation to vapors in painted rooms. Residential exposures resulting from tree injection uses are considered to be negligible. Therefore, aggregate exposures to MBC (and metabolites or concern) resulting from benomyl, thiophante-methyl, and MBC use have been estimated and evaluated in this report.

Hazard: Both benomyl and MBC are of low toxicity following acute oral, dermal and inhalation exposures (toxicity categories IV for oral, inhalation and primary skin irritation, III for dermal). Benomyl is classified as a mild to moderate skin sensitizer, while MBC is not a skin sensitizer. Benomyl is most toxic via the inhalation route of exposure following subchronic exposures, causing adverse respiratory effects in rats. In all animal species, the most sensitive toxicological effect is liver toxicity following subchronic and chronic oral exposure to both benomyl and MBC. MBC is generally more toxic than benomyl. Dogs appear to be the most sensitive species to subchronic and chronic oral exposure. Both benomyl and MBC have been associated with an increased incidence of mouse liver tumors following chronic oral exposure. Both benomyl and MBC have weak mutagenic activity that is primarily attributed to adverse effects on cellular spindle apparatus. In addition, both chemicals cause aneuploidy (i.e., abnormal number of chromosomes) in vivo (in mice following oral dosing) and in vitro.

Both benomyl and MBC induce developmental toxicity in the absence of maternal toxicity in animals, indicating increased fetal susceptibility. Fetal effects from benomyl exposure include ocular malformations, increased mortality, reduced fetal weight, brain malformations, cleft palate and delayed skeletal and visceral maturation. In rats, adverse fetal effects attributed to maternal MBC exposure include decreased body weight, increases in skeletal variations and malformations, and ocular and brain malformations. Both benomyl and MBC are associated with adverse reproductive effects, including effects on the male reproductive system. Adverse testicular effects have been observed in rats, dogs, mice and rabbits exposed to benomyl by oral, dermal and/or inhalation routes of exposure. In addition, MBC has been associated with adverse reproductive effects, including testicular effects following oral exposure. Testicular effects include reduced sperm counts, reduced testes size, and testicular pathology (i.e., atrophy and degeneration of the seminiferous tubules). Other reproductive effects observed only in the presence of parental toxicity include reduced pup weights.

Toxicity Endpoints. The toxicity endpoints used in this document to assess hazards include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and long-term dermal and inhalation doses. HED's Hazard Identification Assessment Review Committee (HIARC) developed toxicity endpoints for both benomyl and its primary metabolite MBC based on exposure concerns. Because benomyl and MBC cause adverse developmental effects, HIARC identified two acute dietary reference doses (aRfDs) for each compound, one for females of the child bearing age (13-50 years) and one for the general population. In addition, HIARC identified chronic RfDs (cRfDs) for both benomyl and MBC.

Acute and Chronic RfDs. For benomyl, HIARC identified aRfDs of 0.3 mg/kg/day and 0.25 mg/kg/day for females (13-50 years) and the general population, respectively. The female (13-50 years) acute RfD is based on an increased incidence of small eyes (microophthalmia) in fetuses in a rat developmental study. The benomyl aRfD for the general population is based on adverse testicular effects following a single dose exposure. The benomyl cRfD of 0.13 mg/kg/day is based on liver toxicity observed in a 2-year dog study. The acute dietary RfDs for MBC are 0.1 mg/kg/day and 0.17 mg/kg/day for females (13-50 years) and the general population, respectively, based on adverse fetal effects and testicular effects, respectively. The chronic RfD of 0.025 mg/kg/day is based on adverse liver effects from a 2-year dog study. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain all acute and chronic RfDs, except for the general population acute RfD for MBC, which has a total uncertainty factor of 300 (extra factor of 3) to account for the absence of a NOAEL.

Dermal Endpoints. For benomyl, HIARC identified a route-specific short- and intermediate-term dermal NOAEL of 500 mg/kg/day from a 21-day dermal rabbit study based on adverse testicular effects. Therefore, a dermal absorption adjustment is not necessary. There are no long-term dermal exposures to benomyl. For MBC, HIARC identified short- and intermediate term NOAELs of 10 mg/kg/day based on adverse fetal effects noted in a rat developmental study. The long-term NOAEL is 2.5 mg/kg/day based on liver toxicity noted in a 2-year dog study. Because oral NOAELs were selected, a 3.5 percent dermal absorption factor, based on a rat dermal absorption study with benomyl was used.

Inhalation Endpoints. The short-, and intermediate- term inhalation NOAEL is 0.96 mg/kg/day from a 90-day rat inhalation study with benomyl that observed adverse respiratory effects at 4.8 mg/kg/day. Due to an absence of inhalation data for MBC, this inhalation NOAEL for benomyl was also used to assess inhalation exposures for MBC for similar durations.

Cancer. Both benomyl and MBC are classified as group C, possible human carcinogens and are associated with hepatocellular tumors in certain strains of mice. HED estimated a unit risk Q_1* of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for both benomyl and MBC based on hepatocellular (adenoma and/or carcinoma) tumors in CD-1 female mice exposed to MBC. Benomyl exposure was adjusted downwards by a factor of 0.66 to account for the difference in molecular weight between MBC and benomyl.

FQPA Safety Factor: The Food Quality Protection Act (FQPA) Safety Factor Committee determined that the FQPA 10X safety factor should be retained. The factor is to be applied to acute and chronic dietary exposures. In accordance with HED policy, a RfD modified by a FQPA safety factor is a population adjusted dose or PAD[1]. The **10X factor was retained for both benomyl and MBC** due to evidence of increased susceptibility following *in utero* exposure of benomyl in the prenatal developmental toxicity study in rats; evidence of increased susceptibility following *in utero* exposure of MBC in the prenatal developmental toxicity study in rats and rabbits; and the need for developmental neurotoxicity studies in rats for both benomyl and MBC.

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[1] PAD= Population Adjusted Dose = $\frac{\text{Acute or Chronic RfD}}{\text{FQPA Safety Factor}}$

The 10x FQPA safety factor is applicable for all **risk assessments for Females (13-50 years), Infants, and Children** (1 - 6 years and 7-12 years).

Relative Potency Factors: HED used relative potency factors (RPFs) to convert benomyl exposures into MBC equivalents in order to aggregate benomyl and MBC non-cancer risk estimates for the target organs of concern. A RPF is derived based on a ratio of the MBC population adjusted dose (PAD) to the benomyl PAD. For acute exposures, RPFs of 0.68 and 0.33 were used to convert benomyl exposures into MBC equivalents for all populations, and females (13-50 years), respectively. For chronic exposures, a RPF of 0.192 was used to convert benomyl exposures into MBC equivalents.

Dietary Exposure: HED has conducted acute and chronic dietary risk assessments for benomyl, and MBC and other the metabolites of concern. HED expresses dietary risk estimates as a percentage of the acute PAD (aPAD) or chronic PAD (cPAD). Dietary exposures that are less than the 100% of the aPAD or cPAD are below HED's level of concern

The acute and chronic dietary risk assessments for benomyl and MBC and other benzimidazole metabolites (2-AB, 5-HBC and 4-HBC) are highly refined (Tier 3) analyses that incorporate percent crop treated information and monitoring data from the U.S. Department of Agriculture's (USDA's) Pesticide Data Program (PDP) for 17 commodities. By translating data, the PDP data were used to assess an additional 82 commodities. The chronic non-cancer dietary analysis indicates no risk estimates of concern for any population subgroup, with chronic dietary risk estimates of 0.6% and 6.7% of the chronic PAD for the highest exposed population subgroup, children 1-6 years of age for benomyl and MBC, respectively. The lifetime cancer risk estimates are $7x10^{-8}$ and $2x10^{-7}$ for benomyl and MBC, respectively. Generally, HED is concerned when cancer risk estimates exceed $1x10^{-6}$ or one-in-one million. The acute dietary risk estimates range from 0.9% to 15% of the acute PAD at 99.9th percentile, for benomyl, with infants <1 years being the highest exposed population subgroup. For MBC, the acute dietary risk estimates range from 4% to 76%, with the highest risk estimates for females (13-50 years), primarily because the aPAD for this subgroup is lower than the aPAD for children. In addition, total benomyl and MBC dietary risks were estimated because the PADs were based on similar effects for both chemicals, and because simultaneous exposure is plausible for these chemicals on food commodities. The highest total non-cancer chronic risk estimate is **7% of the cPAD** for liver effects, for children 1-6 years. The highest acute dietary risk estimate represents **83% of the aPAD** for developmental effects for females of child bearing age (13-50 years). The total **lifetime cancer risk estimate is $3x10^{-7}$**, which is below HED's level of concern.

Water Exposure: The available environmental fate data suggest that benomyl rapidly degrades to MBC in the environment. Benomyl and MBC have a low potential to leach to groundwater in measurable quantities from most typical agricultural uses based on their high soil organic carbon partition coefficients (Koc) of 500 L/kg and 2,100 L/kg, respectively. The available data indicate that the primary metabolite of benomyl, MBC, is less mobile and significantly more persistent in many soils, especially under anaerobic conditions. The Environmental Fate and Effects Division (EFED; memos by R. Pisigan Jr. November 29, 2000, J. Peckenpaugh dated January 14, 1998 and May 4, 1999) has provided a screening-level drinking water assessment using simulation models and an analysis of available monitoring data to estimate the potential concentrations of benomyl

and MBC in ground and surface water. Only MBC was evaluated because benomyl is hydrolytically unstable and is not expected to be detectable in surface and groundwater.

Potential exposures and risks from MBC residues in drinking water were assessed using modeling techniques (Tier 1 SCI-GROW for groundwater and Tier 1 GENEEC for surface water). Inputs to the models included high exposure agricultural scenarios for the major crops (i.e., citrus) with the highest annual benomyl use rate at the maximum application rate of 1.5 lbs ai benomyl/acre with two treatments per year (i.e., 3 lb ai benomyl/acre/year). For risk assessment purposes, groundwater estimated acute and chronic environmental concentrations (EECs) for MBC are both 0.14 µg/L. 56-Day average and peak acute EECs of MBC in surface water using the GENEEC screening model are 2.4 µg/L and 15.8 µg/L, respectively based on the same assumptions.

Aggregate Exposure. As mandated by the FQPA amendments to the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency must consider total aggregate exposure from food, drinking water, and residential sources of exposure to benomyl and MBC. Since benomyl has no registered residential uses, this aggregate assessment will only consider exposure to benomyl and MBC from food and drinking water. However, the Agency has concerns about possible residential exposures from benomyl spray drift. The Agency is currently developing methods to assess residential exposures from spray drift, and these will be assessed in the future when new methods are available. Because both benomyl and MBC have common acute and chronic toxicity endpoints (i.e., developmental, and testicular effects for acute toxicity, and liver effects for chronic toxicity), it is appropriate to add benomyl and MBC dietary risk estimates. In addition, individuals may consume both residues simultaneously on a given commodity because benomyl degrades to MBC. The **acute aggregate benomyl and MBC risk estimates do not exceed HED's level of concern**, since the acute dietary exposure is <100% aPAD, and the acute EECs are less than the acute drinking water level of comparisons (DWLOCs). The **chronic non-cancer aggregate risk estimates do not exceed HED's level of concern** because combined exposure to benomyl and MBC through food and drinking water sources are <100% cPAD (i.e., chronic EECs are less than the chronic DWLOCs). In addition, the total food and drinking water cancer risk estimates for benomyl and MBC are below $1x10^{-6}$ (i.e., chronic/cancer EEC is less than the cancer DWLOC).

HED also conducted an aggregate exposure assessment for MBC resulting from registered uses of benomyl, thiophanate-methyl, and MBC. Although benomyl has no registered residential uses, thiophante methyl, which also degrades to MBC, is registered for residential lawn and home orchard use, and is applied to golf courses. In addition, MBC is registered as a paint additive in residential settings.

The **acute aggregate** MBC exposure from all uses (benomyl and thiophante methyl) and benomyl risk estimates **exceed HED's level of concern for children and females** (13-50 years). **Short- and intermediate-term aggregate risk estimates**, that include MBC and benomyl exposures from diet and MBC residential /non-occupational exposures, result in total risk estimates for MBC and benomyl for children and females (13-50 years) that also **exceed HED's level of concern**. The **chronic non-cancer aggregate** assessment risk estimates **exceed HED's level of concern** for children and females (13-50 years), as the DWLOCs of 18-68 µg/L are less than the long-term MBC EEC of 243 µg/L based on thiophanate-methyl lawn and ornamental use. In

addition, the **aggregate cancer risk estimates** for benomyl and MBC from all uses also **exceed HED's level of concern** because the aggregate dietary, drinking water and residential risks from MBC are greater than $1x10^{-6}$ (i.e., cancer DWLOC of 1.4 µg/L is less than the long-term EECs of 2.4 to 243 µg/L).

In accordance with current OPP policy (S. Johnson 11/17/97), if the EECs exceed the DWLOCs, water monitoring data are required to refine the drinking water exposure estimate. SRRD and EFED should determine the nature and extent of the water monitoring data required.

The Agency is in the process of formulating guidance for conducting cumulative risk assessment. When the guidance is finalized, benomyl and other compounds with similar mechanism of toxicity will be revisited to assess the cumulative effects of exposure to multiple compounds.

Occupational Exposure: Occupational exposures to benomyl can occur during handling, mixing, loading and application activities. Because environmental fate data suggest that the benomyl rapidly converts to MBC, all postapplication residues were assumed to be MBC. Occupational postapplication exposure to MBC can occur for agricultural workers during scouting, irrigation, cultivation, harvesting and handling seeds and seedlings.

Based on toxicological criteria and potential for exposure, HED has conducted dermal and inhalation exposure assessments for occupational handlers exposed to benomyl and dermal exposure assessments for occupational postapplication exposures to MBC. Inhalation is not expected be a significant postapplication exposure route, except for possibly handling treated seeds for planting, for which no data are available. The duration of exposure is expected to be short-, and intermediate-term for the occupational handler, and short-, intermediate- and long-term for occupational postapplication exposures during agricultural and harvesting activities. The exposure duration for short-term assessments is 1 to 7 days. Intermediate-term durations are 1 week to 6 months, and long-term exposures are durations greater than 6 months. For dermal and inhalation risk assessment, risk estimates are expressed in terms of the Margin of Exposure (MOE), which is the ratio of the NOAEL selected for the risk assessment to the exposure. For occupationally exposed workers, MOEs $\geq$100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) for dermal and inhalation exposures are considered to be below the Agency's level of concern. An aggregate dermal and inhalation MOE was not calculated because the toxicity endpoint differs between dermal (testicular effects) and inhalation (respiratory effects) exposures.

Occupational risk estimates for handlers exposed to benomyl do not exceed HED's level of concern with label-required PPE or engineering controls. The results of the short- and intermediate-term agricultural handler assessments indicate that most of the potential exposure scenarios provide dermal and inhalation MOEs greater than or equal to 100 at baseline attire (i.e., long pants, long sleeved shirts, no gloves), while all of the 8 major scenarios quantitatively evaluated using label-required personal protective equipment (PPE) (long sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves) or by using engineering controls (e.g., water soluble bags) have MOEs greater than or equal to 100. Benomyl handler total cancer risk estimates (dermal and inhalation combined) are in the range of $4x10^{-9}$ to $3x10^{-5}$ for baseline attire for private handlers and $1x10^{-8}$ to $1x10^{-4}$ for commercial handlers. All cancer risk estimates were below $1x10^{-6}$ with label-required PPE and/or engineering controls, except scenario (7) mixing,

loading and applying benomyl as an on-farm seed treatment in a planter box, where the commercial cancer risk estimate is $6x10^{-6}$. There are insufficient data to assess the commercial seed/seedling treatment uses, or dip treatments, and additional data are requested to support these uses. The agricultural handler assessments are believed to be reasonable representations of benomyl uses. Surrogate pesticide PHED data were used to assess handler exposure except for treatment of mushrooms with benomyl (i.e., mixing/loading/applying using pressurized tank with sprinkler hose), for which a chemical-specific exposure study was available and the dry plant box seed treatment, for which a published study was used as a surrogate.

The results of the short-, and intermediate-term dermal **postapplication assessments** for workers exposed to MBC at agricultural use sites indicate that the current Worker Protection Standard (WPS)-required restricted entry interval (REIs) of 24 hours is adequate. The potential for dermal contact during postapplication activities (e.g., harvesting) is assessed using a matrix of potential dermal contact rates by activity. Chemical-specific postapplication exposure Dislodgable Foliar Residue (DFR) data were submitted for apples, grapes, strawberries and mushrooms. These data were used along with HED standard transfer coefficients derived using recently submitted Agricultural Re-entry Task Force (ARTF) data, to assess potential exposures to workers reentering treated sites. The estimates showed that short- and intermediate-term dermal post-application worker exposures to MBC resulted in MOEs of greater than 100 on the first day after application of benomyl for all crops and activities, and therefore do not exceed HED's level of concern. Long-term (greater than 180 days/year) MOEs for harvesting mushrooms, strawberries, blueberries, tomatoes, and pineapples are also greater than 100. Dermal cancer risk estimates for all post-application scenarios were less than $1x10^{-5}$ at 7 days after treatment (range of $<5x10^{-8}$ to $9x10^{-6}$). The occupational postapplication assessment is believed to be reasonably representative of benomyl uses. The long-term post application scenarios are considered conservative high-end estimates and are sufficient for a screening-level exposure and risk assessment. While some individuals exposure may exceed these estimates, the Agency believes that most workers in each group would have fewer than 180 days of exposure, as assessed for the indicator crops.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Benomyl (CAS Registry No.:17804-35-2), has an empirical formula of $C_{14}H_{18}N_4O_3$, and a molecular weight of 290.3. It is a white crystalline solid which decomposes without melting upon heating. Benomyl is essentially insoluble in water (2 mg/L), but is soluble in chloroform (9.4 g/100 g) and dimethylformamide (5.3 g/100 g), and sparingly soluble in acetone (1.8 g/100 g), xylene (1 g/100 g) and ethanol (0.4 g/100 g) at 25° C. Benomyl undergoes decomposition on exposure to moisture.

The HED Metabolism Committee has determined that the residues of concern in plant commodities include benomyl and its metabolites containing the benzimidazole moiety, MBC, 2-AB, 5-HBC and 4-HBC. The chemical names and structures of the residues of concern are depicted in Figure A.

Figure A. Chemical structures of benomyl residues of concern.

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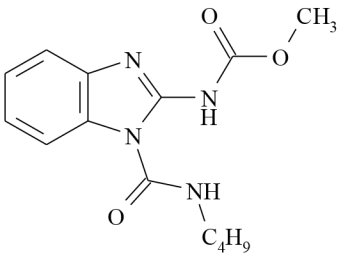
<td> 
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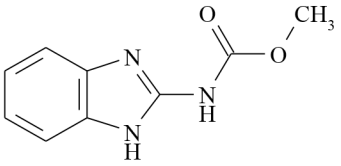
<td> 
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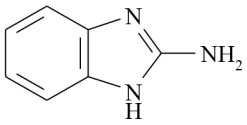
<td> 
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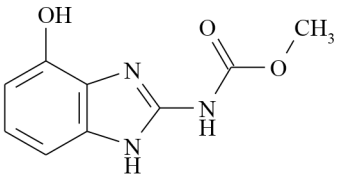
<td> 
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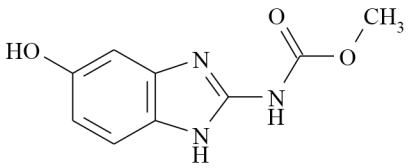
<td> 
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Benomyl rapidly degrades to carbendazim (MBC) in surface water. MBC is also a white solid that has a molecular weight of 191.2 and is not very soluble in water (8 mg/L at pH of 7). MBC is more stable than benomyl, especially under aerobic conditions. MBC has a typical aerobic soil

metabolism half life ($T_{½}$) of 320 days and aerobic and anaerobic aquatic metabolism half lives of 61 and 743 days, respectively (Memorandum from J. Peckenpaugh to D. Smegal, Revision in Drinking Water Assessment for Benomyl, May 4, 1999). The soil/water partition coefficient (K_{oc}) values for benomyl and MBC are 500 L/kg and 2,100 L/kg, indicating that both compounds are not very mobile in soils. MBC is not volatile based on its low vapor pressure of $1x10^{-7}$ mmHg at 20° C.

There is only one benomyl manufacturing-use product (MP), the 95% technical (T; EPA Reg. No. 352-377), which is registered to E.I. du Pont de Nemours and Company, Incorporated. All pertinent product chemistry data requirements are satisfied for the du Pont benomyl Technical Grade Active Ingredient (TGAI); however, additional data are required concerning enforcement analytical methods (GLN 830.1800) for the 95% T. Provided that the registrant either certifies that the suppliers of beginning materials and the manufacturing process for the benomyl T have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of benomyl with respect to product chemistry data requirements.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile Overview

The toxicology data in support of benomyl reregistration are complete in accordance with the Subdivision F Test Guidelines for a food use chemical and adequate to assess the health hazards resulting from exposure to benomyl. The Hazard Identification Assessment Review Committee (HIARC) has requested a developmental neurotoxicity (DNT) study in rats for benomyl. Toxicology data for carbendazim (Methyl 2-Benzimidazole Carbamate) or MBC, the primary environmental breakdown product of benomyl, are also considered in this assessment. In foods and the environment, benomyl rapidly transforms to MBC, hence environmental residues are primarily MBC. MBC is also registered for use as a systemic carbamate fungicide, but has no registered food uses in the US. The HIARC requested two toxicity studies with MBC, a 21 day dermal toxicity study in rats and a developmental neurotoxicity study in rats. In addition, the 2-generation rat reproduction and subchronic studies for MBC fail to meet the Subdivision F Guidelines. The available toxicology studies are summarized in Appendix A (Tables A-1 and A-2 for benomyl and MBC, respectively).

Acute Toxicity. Both benomyl and MBC are of low toxicity following most acute exposures. Guideline studies for acute toxicity indicate that both chemicals are classified as category IV for acute oral and inhalation toxicity, category III for acute dermal toxicity, and category IV for primary skin irritation. Benomyl is in category II, while MBC is in category III for primary eye irritation. Benomyl is classified as a mild to moderate skin sensitizer, while MBC is not a skin sensitizer. Acute toxicity values and categories for the technical grade of benomyl and MBC are summarized on Tables 1 and 2, respectively.

Subchronic Toxicity. Several subchronic studies are available for benomyl including one oral study in rats, mice and dogs, a 21 day dermal toxicity study in rabbits, and a 90-day inhalation study in rats. All three oral studies (in rats, mice and dogs) fail to meet the test guidelines, however, chronic mouse and dog studies are available to satisfy these guidelines. Benomyl is

most toxic following subchronic inhalation exposures and causes respiratory effects characterized by cell necrosis, chronic and acute inflammation and loss of olfactory epithelium with foci of repair in rats exposed to doses as low as 4.8 mg/kg/day (50 mg/m^3). In all animal species the most sensitive toxicological endpoint following subchronic oral exposure is liver toxicity manifested as induction of liver enzymes accompanied by liver cell hypertrophy and proliferation and increased liver weight at doses as low as 62.5 mg/kg/day. Dogs appear to be the most sensitive species following subchronic oral exposure to benomyl. Rabbits dermally exposed to benomyl dose levels at and above 1000 mg/kg exhibited diarrhea, oliguria and hematuria. Biologically significant effects on testicular weight were also noted following dermal exposure to 1000 mg/kg.

Only one subchronic oral study in dogs was available for MBC. Although classified as unacceptable, both liver and testicular effects were noted at MBC doses as low as 35-40 mg/kg/day.

Chronic Toxicity and Carcinogenicity. Benomyl and MBC were evaluated for carcinogenic potential in both rats, and mice. In addition, benomyl and MBC were evaluated for chronic toxicity in dogs. In all species (except rats treated with benomyl), the most sensitive toxicological endpoint is liver toxicity that occurred at levels as low as 62.5 mg/kg/day for benomyl and 12.5 mg/kg/day for MBC, indicating that MBC may be more toxic than benomyl following chronic exposure. Dogs appear to be the most sensitive species for liver toxicity following chronic oral exposure to both fungicides. For benomyl, liver effects were characterized by hepatic cirrhosis, bile duct proliferation with corresponding biochemical changes indicative of liver injury. Testicular degeneration was noted in dogs at benomyl doses as low as 62.5 mg/kg/day, and in mice at much higher doses of 1125/750 mg/kg/day.

Both benomyl and MBC are classified in group C (possible human carcinogens) because they induced liver tumors (hepatocellular adenoma and/or carcinomas) in mice. There is no evidence of carcinogenicity in rats for either fungicide. HED calculated a Q_1* of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for both benomyl and MBC based on a mouse carcinogenicity study with MBC that observed statistically significant increases in liver adenomas and carcinomas in females (Wood et al. 1982). The Q_1* was calculated using the $(mg/kg/day)^{3/4}$ cross species scaling factor. This Q1* was determined to be appropriate for both benomyl and MBC. It is noted that the benomyl and MBC rat studies only tested 36 rats/sex/dose (and only 20/sex/dose in the 250 mg/kg/day MBC highest dose group), when current guidelines require 50 rats/sex/dose.

Developmental Toxicity. Both benomyl and MBC induce developmental toxicity in the absence of maternal toxicity in rats or with minimal toxicity in rabbits. Benomyl was evaluated for developmental toxicity in rats and rabbits in registrant-submitted studies. In rats, developmental effects were noted at doses ranging from 62.5 to 125 mg/kg/day in the absence of maternal toxicity, indicating increased fetal sensitivity. At 62.5 mg/kg/day developmental effects included increased incidence of ocular malformations (microphthalmia and anophthalmia), increased fetal mortality and reduced fetal weight. Effects at 125 mg/kg/day included increased incidence of malformations of the brain, characterized by distended lateral ventricles and hydrocephaly. Fetuses of rabbit does exposed to 180 mg/kg/day developed a significantly increased incidence in visceral variations (small renal papillae) that were not readily attributed to exposure and were not considered to be malformations because they may have occurred as a result of incomplete

maturation. Nevertheless, the visceral variations occurred at maternally toxic doses as indicated by stained tails and reduced feed consumption at 180 mg/kg/day.

Literature studies have also demonstrated that benomyl induces developmental effects in rats and mice following gavage administration to pregnant animals at doses as low as 62.5 mg/kg/day and 100 mg/kg/day, respectively (Kavlock et al. 1982, Chernoff 1985). Developmental effects in rats include small eyes (microphthalmia), decreased fetal weight, increased fetal mortality and delayed skeletal and visceral maturation, while effects in mice include cleft palate, supernumerary ribs and subnormal vertebral centrum (no compound-related microphthalmia was reported). Literature studies have also demonstrated a difference in fetal response to gavage versus dietary exposure to benomyl, with gavage dosing producing anomalies at approximately one-tenth of the dietary dose (Kavlock et al. 1982, Chernoff 1985). In addition, literature studies suggest that the incidence and severity of the developmental effects appear to be increased when the dams are nutritionally comprised (protein deficient) and by late gestation dosing.

Benomyl has also been associated with sustained adverse effects on the male reproductive system (decreased weight of testes, prostate, and seminal vesicles) in a postnatal rat study at doses as low as 31.2 mg/kg/day (Kavlock et al. 1982).

There is increased sensitivity of rat and rabbit fetuses as compared to maternal animals following *in utero* exposure to MBC, in prenatal developmental toxicity studies. In the MBC rat study, increased sensitivity manifested as developmental anomalies [decreased fetal body weight and increases in skeletal variations and a threshold for malformations, i.e., some malformations noted but not statistically significant) at doses of 20 mg/kg/day which were not maternally toxic. At higher doses of 90 mg/kg/day, treatment-related malformations of the CNS were observed which included exencephaly, domed head, anophthalmia, microphthalmia and bulged eyes. For developmental toxicity the NOAEL was 10 mg/kg/day, whereas for maternal toxicity, the NOAEL was 20 mg/kg/day (based on a slight increase in liver weight at 90 mg/kg/day).

In the rabbit developmental study with MBC, increased sensitivity manifested as decreased implantations and litter size, and increased resorptions at 20 mg/kg/day; the NOAEL is 10 mg/kg/day. Maternal toxicity was not observed until higher doses of 125 mg/kg/day, based on abortions and decreased maternal body weight; the maternal NOAEL is 20 mg/kg/day.

Reproductive Effects. Both benomyl and MBC are associated with adverse reproductive effects, including effects on the male reproductive system. Benomyl induced reproductive toxicity in rats, but only at dose levels that induced parental toxicity. Reproductive effects included reduced pup weights and testicular pathology, while parental effects included decreased sperm counts as well as histological lesions of the testes (atrophy and degeneration of the seminiferous tubules) at doses as low as 168 mg/kg/day.

Adverse testicular effects have been observed in rats, dogs, mice and rabbits exposed to benomyl by oral (gavage and dietary), dermal and inhalation routes in registrant-submitted and literature studies. Testicular effects (decreased spermatogenesis) were observed in acute LC_{50} studies in both rats and dogs 14 days following a single 4-hour inhalation exposure at doses of 33 mg/kg (0.82 mg/L) and 82 mg/kg (1.65 mg/L), respectively. The acute inhalation NOAELs were 7.5 mg/kg (0.2 mg/L) and 32 mg/kg (0.65 mg/L) for rats and dogs, respectively. Testicular effects

(decreased size of the testes, lesions, degeneration) were also noted in the 1992 acute neurotoxicity study in rats, and in the 1982 mouse oncogenicity study. Literature studies have also reported testicular effects 2 days and 70 days post exposure in adult male rats given single gavage doses of benomyl as low as 50 and 100 mg/kg, respectively. Effects include dose-dependent increases in the premature release of germ cells (sloughing), seminiferous tubular atrophy and occluded efferent ductules (Hess et al. 1991). Male offspring in a postnatal rat study (dams dosed from gestation day 7 to lactation day 15) exhibited testicular effects, including permanent reductions in testes weight, and ventral prostate and seminal vesicles at 31.2 mg/kg.

MBC was associated with adverse reproductive effects (decreased birth weight at weaning) in an unacceptable reproductive toxicity study in rats. MBC also caused adverse testicular effects characterized by premature release of immature germ cells, atrophy of a few seminiferous tubules and significant decrease in seminiferous tubule diameter following a single gavage dose with 50 mg/kg (Nakai et al. 1992). In addition, evidence of testicular effects has been demonstrated in the unacceptable 90-day subchronic dog study with MBC.

Mutagenicity. Both benomyl and MBC have marginal mutagenic activity in standard in vitro studies. In contrast, there is clear and reproducible evidence of aneuploidy (i.e., abnormal number of chromosomes) both in vitro and in vivo. There is also convincing evidence that the induction of aneuploidy by benomyl and MBC is primarily attributed to adverse effects on cellular spindle apparatus. Both benomyl and MBC are established spindle poisons that induce aneuploidy effects in both in vitro and in vivo test systems. For example, nondisjunction was reported in A. nidulans and many other test systems with both agents. Both fungicides also produced positive effects in bone marrow antikinetochore micronucleus assays, which were consistent with a spindle effect. However, neither compound is clastogenic. Since the genotoxic activity of benomyl and MBC is well known, these pesticides are frequently used as test chemicals (i.e., positive controls) for the assessment of new assay systems for the detection of aneuploidy induction.

In mutagenicity studies with benomyl and MBC, there is compelling evidence of aneuploidy induction following oral dosing in mice. Mutagenicity data support the evidence of developmental anomalies in rats and hepatocellular tumors in several strains of male and female mice.

Neurotoxicity. No treatment-related neurotoxicity was observed in the acute or subchronic rat studies with benomyl. Although increased motor activity was noted at the highest dose tested (456-578 mg/kg/day) in the benomyl subchronic rat study, this observation was discounted due to the presence of systemic toxicity. However, functional effects were not measured in this study. Benomyl and MBC do not appear to cause delayed neurotoxicity in hens. The benomyl prenatal developmental toxicity study in rats demonstrated central nervous system (CNS) anomalies in the fetuses following maternal exposure during gestation. The CNS anomalies included anophthalmia, microophthalmia and hydrocephaly. Developmental CNS malformations were also noted in the MBC prenatal developmental toxicity study in rats, which included exencephaly, domed head, anophthalmia, microophthalmia and bulged eyes.

Metabolism/Pharmacokinetic Studies. In the rat, benomyl and MBC are excreted primarily in the urine with lesser amounts excreted in the feces, and MBC is poorly distributed to the tissues.

MBC was rapidly absorbed and extensively metabolized in CD/BR rats following single oral doses up to 1000 mg/kg. The half-life of MBC was approximately 12 hours, and 98% of carbendazim was excreted by 72 hours post- administration. The primary reactions involved in the metabolism of MBC were oxidation of the phenyl ring, followed by conjugation to yield sulfate and glucoronide conjugates of 5-hydroxycarbendazim and 5,6-dihydroxycarbendazim. Subsequent phenyl ring oxidation and N-oxidation at the imidazole nitrogen led to significant levels of 5,6-hydroxy-oxo-carbendazim N-oxide glucuronide conjugate, especially in female rats.

Dermal Absorption. The dermal absorption of benomyl is low and ranges from 0.031 to 3.5 percent in rats for 100 mg or 0.1 mg ai benomyl, respectively. A dermal absorption factor of 3.5% was used in risk assessment. HED recently reviewed new data pertaining to dermal absorption (MRID 45150601-45150610) and concluded that the dermal absorption factor of 3.5% is appropriate (memo from R. Zendzian to D. Smegal, December 6, 2000, D267438).

Mechanism of Action. In 1997, the HED RfD/Peer Review Committee summarized a mechanism of action for benomyl. The following summary is an excerpt from the 5/28/97 report. "Benomyl has been reported to inhibit the in vitro polymerization of the rat neurotubulin at approximately 7.5 µg/mL (Albertini et al. 1993). This finding is consistent with the known mechanism of aneuploidy induction by the benzimidazole class of compounds (i.e., in vitro inhibition of yeast and/or mammalian tubulin polymerization with impairment of the spindle apparatus and resulting aneuploidy in the daughter cells) (Albertini et al. 1988).

Since it is generally acknowledged that somatic cell aneuploidy may be in involved in carcinogenesis and that the genetic imbalances resulting from aneuploidy in germinal cells may contribute to birth defects, it is not surprising that the results from genetic toxicology testing with benomyl correlate with the data from chronic feeding studies demonstrating hepatocellular carcinomas in male and female mice. Similarly, the genetic toxicology data support the evidence of developmental effects in rats. Hoogenboom et al. (1991) postulated that the known antitubulin action of benomyl may impair microtubule formation and produce brain and ocular malformations by disruption of neuronal proliferation and migration.

Other metabolites. The primary metabolites of MBC are 5-hydroxy-2-benzimidazolecarbamic acid, methyl ester (5-HBC) and 2-aminobenzimidazole (2-AB). The acute toxicity of 5-HBC and 2-AB could not be compared to MBC since they were not tested at levels higher than 3400 and 7500 mg/kg, respectively. MBC did not cause death in rats following single oral doses of 5000 mg/kg. Deaths (6/6) occurred with 2-AB following 10 doses at 670 mg/kg/day (2/6 occurred with MBC at 3400 mg/kg/day). 5-HBC was not tested higher than 200 mg/kg/day for 10 doses over 2 weeks. Testicular degeneration was observed with 5-HBC at 3400 mg/kg but not with 2-AB up to 7500 mg/kg.

Table 1 Acute Toxicity of Benomyl					
Guideline No.	**Study Type**	**% a.i.**	**MRID #**	**Results**	**Toxicity Category**
870.1100 (81-1)	Acute Oral, Rat	75	00064819	LD_{50} = >5000 mg/kg,	IV
870.1200 (81-2)	Acute Dermal, Rabbit	75	243043	LD_{50} = >2000 mg/kg,	III
870.1300 (81-3)	Acute Inhalation, Rat	50	00097599	LC_{50} >4.01 mg/L	IV
870.2400 (81-4)	Primary Eye Irritation, Rabbit	75	00064820	irritant	II
870.2500 (81-5)	Primary Skin Irritation, Rabbit	75	243043	Non-irritant	IV
870.2600 (81-6)	Dermal Sensitization, Guinea Pig	not given	050427	mild to moderate dermal sensitizer	N/A
870.6100a (81-7)	Delayed neurotoxicity, hen	not given	241930	NOAEL = 2500 mg/kg	N/A
870.6200a (81-8)	Acute Neurotoxicity, Rat	97.4	42817003	NOAEL >2000 mg/kg	N/A

N/A Not applicable

MBC is of low toxicity following acute exposures. Guideline studies for acute toxicity indicate that the carbendazim is classified as category IV for acute oral toxicity, category III for acute dermal and inhalation toxicity and primary eye irritation, and category IV for primary skin irritation. MBC is not a skin sensitizer, and there is no evidence of delayed neurotoxicity in hens. Acute toxicity values and categories for carbendazim are summarized in the following table.

Table 2 Acute Toxicity of MBC					
Guideline No.	**Study Type**	**% a.i.**	**MRID or Accession No.**	**Results**	**Toxicity Category**
870.1100 (81-1)	Acute Oral, Rat	98	256025 (Acc No)	LD_{50} = >10,000 mg/kg,	IV
870.1200 (81-2)	Acute Dermal, Rabbits	75 INE 965	256025 (Acc No)	LD_{50} = >2,000 mg/kg formulation	III
870.1300 (81-3)	Acute Inhalation, Rat	75 INE 965	256025 (Acc No)	LC_{50} >5 mg/L	IV
870.2400 (81-4)	Primary Eye Irritation, Rabbit	>98	256025 (Acc No)	minimal to no irritation	III

Table 2 Acute Toxicity of MBC					
Guideline No.	**Study Type**	**% a.i.**	**MRID or Accession No.**	**Results**	**Toxicity Category**
870.2500 (81-5)	Primary Skin Irritation, Rabbit	75 INE 965	256025 (Acc No)	slight irritation at 24 hr, normal by 72 hr	IV
870.2600 (81-6)	Dermal Sensitization, Guinea Pig	98	256025 (Acc No)	not a dermal sensitizer	N/A
870.6100a (81-7)	Delayed neurotoxicity, hen	Not given	241931 (Acc No)	NOAEL = 2500 mg/kg	N/A

N/A Not applicable

3.2 FQPA Considerations

The HED FQPA Safety Factor Committee met on June 7, 1999 to evaluate the hazard and exposure data for benomyl and its primary metabolite, MBC, and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) should be retained at 10X in assessing the risk posed by these chemicals. The FQPA SFC concluded (See memo from B. Tarplee July 1, 1999 HED Do No. 013544) that the FQPA safety factor be retained at 10X for benomyl and its primary metabolite, MBC, due to:

- evidence of increased susceptibility following *in utero* exposure of benomyl in the prenatal developmental toxicity study in rats;
- evidence of increased susceptibility following *in utero* exposure of carbendazim, the primary metabolite of benomyl, in the prenatal developmental toxicity study in rats and rabbits; and
- the need for developmental neurotoxicity study in rats for both benomyl and carbendazim.

The Committee determined that 10X FQPA safety factor for benomyl and its primary metabolite, carbendazim, is applicable for the following subpopulations:

- Females (13-50 years) since increased susceptibility was demonstrated following *in utero* exposure and
- Infants, Children (1 - 6 years), and Children (7 - 12 years) due to the uncertainty resulting from data gaps for the developmental neurotoxicity study in rats.

The Committee determined that 10X FQPA safety factor for benomyl and its primary metabolite, carbendazim, is applicable for the following risk assessment scenarios:

- all risk assessments (acute/chronic dietary and residential scenarios for all durations) since increased susceptibility was seen following *in utero* exposure

(which could occur after a single dose) and since there is uncertainty resulting from the need for developmental neurotoxicity study in rats. This study may provide data that could be used in the toxicology endpoint selection for dietary and nondietary exposure risk assessments.

3.3 Dose-Response Assessment

3.3.1 Non-Cancer Endpoints

On June 1, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to reassess the acute and chronic dietary, and dermal and inhalation endpoints for risk assessment for benomyl, and its primary metabolite carbendazim (MBC). The Committees decisions are presented in the HIARC memorandum dated August 2, 1999 (D. Smegal to S. Knizner, HED Doc No. 013602). To assess dietary exposure, HIARC developed acute and chronic RfDs for both benomyl and its primary metabolite MBC based on exposure concerns. Because benomyl and MBC cause developmental effects, HIARC developed two acute dietary RfDs (aRfD) for each compound, one for females of the child bearing age (13-50 years) and one for the general population. In addition, HIARC developed chronic RfDs (cRfD) for both benomyl and MBC.

Benomyl

For benomyl, HIARC identified aRfDs of 0.3 mg/kg/day and 0.25 mg/kg/day for females (13-50 years) and the general population, respectively. The female 13+ aRfD is based on a NOAEL of 30 mg/kg/day from a rat developmental study that observed an increased incidence of microophthalmia at 62.5 mg/kg/day (LOAEL) in pregnant rats given oral administrations of benomyl at during gestation days 7 through 16. The benomyl aRfD for the general population is based on a NOAEL of 25 mg/kg/day for effects on the male reproductive system [biologically significant premature release of germ cells (sloughing) in the testes, and occlusions of the efferent ductules of the testis 2 days post exposure.] The benomyl cRfD of 0.13 mg/kg/day is based on an oral NOAEL of 12.5 mg/kg/day from a 2-year dog study that observed hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption at 62.5 mg/kg/day. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs.

For benomyl, HIARC identified a route-specific short- and intermediate-term dermal NOAEL of 500 mg/kg/day from a 21-day dermal rabbit study based on decreases in relative and absolute testes weights at 1000 mg/kg/day (LOAEL). Therefore, a dermal absorption adjustment is not necessary. This dermal NOAEL is protective of developmental effects (i.e., oral developmental NOAEL of 30 mg/kg/day ÷ 3.5% dermal absorption is equivalent to an adjusted dermal developmental NOAEL of 860 mg/kg/day). The long-term dermal NOAEL is 12.5 mg/kg/day from a 2 year oral dog study that observed hepatic cirrhosis, clinical chemistry alterations and decreased weight gain and food consumption at 12.5 mg/kg/day. Because an oral NOAEL was selected, a 3.5 percent dermal absorption factor was used. Dermal absorption was estimated to be 3.5 percent based on a rat dermal absorption study.

For benomyl, the short-, intermediate- and long-term inhalation NOAEL is 0.96 mg/kg/day from

a 90-day rat inhalation study with benomyl that observed olfactory degeneration in the nasal cavity at 4.8 mg/kg/day.

MBC

The acute dietary RfDs for MBC are 0.1 mg/kg/day and 0.17 mg/kg/day for females (13-50 years) and the general population, respectively. The female 13+ aRfD is based on a NOAEL of 10 mg/kg/day from a rat developmental study that observed decreased fetal body weight and increases in skeletal variations and a threshold for malformations at 20 mg/kg/day (LOAEL). The aRfD for the general population is based on a LOAEL of 50 mg/kg/day for effects on the male reproductive system [sloughing (premature release) of immature germ cells 2 days post exposure, atrophy of a few seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter, and slight abnormal growth of the efferent ductules at 70 days post exposure]. The cRfD of 0.025 mg/kg/day is based on an oral NOAEL of 2.5 mg/kg/day from a 2-year dog study that observed histopathological lesions of the liver and chronic hepatitis in both sexes at a dose level of 12.5 mg/kg/day (LOAEL). An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs, except for the general population acute RfD, which has a total uncertainty factor of 300 (extra factor of 3) to account for the absence of a NOAEL.

For MBC, HIARC identified short- and intermediate term dermal NOAELs of 10 mg/kg/day from a rat developmental study that observed adverse fetal effects at 20 mg/kg/day (LOAEL) for females (13-50 years). The long-term dermal NOAEL is 2.5 mg/kg/day from a 2-year dog study that observed liver toxicity at 12.5 mg/kg/day (LOAEL). Because oral NOAELs were selected, a 3.5 percent dermal absorption factor, based on a rat dermal absorption study with benomyl was used.

Due to an absence of inhalation data for MBC, the inhalation NOAEL of 0.96 mg/kg/day for benomyl based on respiratory effects was also used to assess inhalation exposures for MBC for all durations.

Population Adjusted Doses

The Population Adjusted Dose (PAD) is the term that OPP is now using to describe a reference dose (RfD) – either acute or chronic– that has been adjusted to take into account the FQPA Safety Factor. PAD (acute or chronic) = RfD (acute or chronic) ÷ FQPA Safety Factor. These PADs are referred to as aPAD and cPAD, respectively.

Depending on the determinations of the HED FQPA SFC, the FQPA safety factor may be the same or different for acute and chronic risk assessments, and may apply to either designated or all population subgroups. For benomyl and MBC, the FQPA safety factor of 10 was retained for acute and chronic dietary risk assessments and all residential assessments, and applies only to the females (13-50 years) and infants, children (1 - 6 years), and children (7 - 12 years) subgroups. The doses and toxicological endpoints selected for various exposure scenarios and subgroups for benomyl and MBC are summarized in Tables 3 and 4, respectively.

3.3.2 Classification of Carcinogenic Potential

Both benomyl and MBC are classified as group C (possible human carcinogens) by the Cancer Peer Review Committee. On 5/21/86, the Scientific Advisory Panel (SAP) concurred with the classification of benomyl. The rationale for this classification is as follows: (1) the carcinogenic response for both benomyl and MBC are confined solely to the mouse liver, even with repeated experiments; (2) the liver tumors produced by benomyl and MBC were observed in 2 related strains of mice (CD-1 and Swiss SPF) know to have high background incidence rates of liver tumors, whereas no liver tumors were produced by MBC in another strain of mice [NMRKf (SPF 71)] known to have a low background incidence rate of liver tumors; (3) benomyl and MBC produced weak mutagenic effects consistent with spindle poison activity rather than gene mutation or DNA repair activity.

The Cancer Peer Review Committee noted the occurrence of mostly malignant hepatocellular tumor response with MBC in two stains of mice, and the presence of unusually occurring and malignant hepatoblastomas with MBC in male SPF Swiss mice. In addition, the mutagenicity information indicates that the aneuploidy known to be produced by benomyl could theoretically result in a loss of tumor suppressor genes and a potential oncogenic effect.

HED estimated a unit risk Q_1^* of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for both benomyl and MBC (memorandum from L. Brunsman to D. Smegal, November 18, 1999, HED Doc no 013859). This estimate is based on the outcome of the re-evaluation of the hepatocellular (adenoma and/or carcinoma) tumors in CD-1 female mice with dose levels of 0, 500, 1500 or 7500 ppm MBC (Wood et al. 1982). The Q_1^* was estimated using the $(mg/kg/day)^{3/4}$ species scaling factor. Details of the quantitative estimate are presented in the Toxicity Memorandum (D. Smegal to D. Fuller, January 31, 2001, D272369). In September 2000, the Ad Hoc Carcinogen Assessment Review Committee (CARC) concluded that benomyl exposure should be adjusted to MBC equivalents by multiplying by a factor of 0.66, which is the ratio of MBC and benomyl molecular weights (D. Smegal to D. Fuller, September 21, 2000, D269149).

Table 3 Summary of Doses and Toxicological Endpoints for Benomyl			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF* and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary, Females 13-50 years	NOAEL=30 mg/kg/day UF = 100 **Acute RfD=** 0.3 mg/kg/day	FQPA SF = 10 **aPAD**= acute RfD / FQPA SF **= 0.03 mg/kg/day**	Rat Developmental Study with Benomyl LOAEL= 62.5 mg/kg/day based on increased incidence of small eyes (microophthalmia) in fetuses of pregnant rats given benomyl during gestation days 7 through 16.
Acute Dietary, General Population	NOAEL=25 mg/kg/day UF = 100 **Acute RfD=** 0.25 mg/kg/day	FQPA SF = 10 (infants and children) **aPAD**= acute RfD / FQPA SF = 0.025 mg/kg/day (infants and children) = 0.25 (general population)	Single Dose Rat Study (Hess et al. 1991) LOAEL= 50 mg/kg/day based on adverse testicular effects including biologically significant premature release of germ cells (sloughing) in the testes, and occlusions of the efferent ductules of the testis 2 days post exposure.
Chronic Dietary	NOAEL=12.5 mg/kg/day UF = 100 **Chronic RfD=** 0.13 mg/kg/day	FQPA SF = 10 (children and females 13-50 yrs) **cPAD**= chronic RfD / FQPA SF = 0.013 mg/kg/day (children and females) = 0.13 (general population)	2 year dog study with benomyl LOAEL= 62.5 mg/kg/day based on hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption .
Short-and Intermediate Term Dermal	Dermal NOAEL = 500 (b)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	21 Day Dermal Rabbit Study LOAEL=1000 mg/kg/day based on decreases in relative and absolute testes weights.
Long-Term Dermal (a)	Oral NOAEL =12.5 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	2 year dog study with benomyl LOAEL= 62.5 mg/kg/day based on hepatic cirrhosis, clinical chemistry alterations as well as decreased weight gain and food consumption.
Short-, Intermediate- and Long Term Inhalation	Inhalation NOAEL= 0.96 (10 mg/m^3)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	90 day rat inhalation study LOAEL=4.8 mg/kg/day (50 mg/m^3) based on olfactory degeneration in the nasal cavity.
Cancer	Q1* = 2.39x10^{-3} (mg/kg/day)$^{-1}$ (c)	Q1* = 2.39x10^{-3} (mg/kg/day)$^{-1}$ (c)	2 year mouse study with MBC, based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice.

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.
UF = Uncertainty Factor

PAD = Population Adjusted Dose (includes UF and FQPA safety factor)
LOC= Level of Concern
MOE= Margin of Exposure

(a) Since an oral value was selected, 3.5% dermal absorption factor should be used for route-to-route extrapolation.

(b) This dermal NOAEL is protective of developmental effects (i.e., oral developmental NOAEL of 30 mg/kg/day ÷ 3.5% dermal absorption is equivalent to an adjusted dermal developmental NOAEL of 860 mg/kg/day).

(c) Benomyl exposures were adjusted to MBC equivalents based on a factor of 0.66, which is the ratio of molecular weights for MBC (190) and benomyl (290) (i.e., multiply benomyl exposure by 0.66).

Table 4
Summary of Doses and Toxicological Endpoints for MBC

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary, Females (13-50 years)	NOAEL=10 mg/kg/day UF = 100 **Acute RfD=** 0.1 mg/kg/day	FQPA SF = 10 **aPAD**= acute RfD / FQPA SF = 0.01 mg/kg/day	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams
Acute Dietary, General Population	LOAEL=50 mg/kg/day UF = 300 **Acute RfD=** 0.17 mg/kg/day	FQPA SF = 10 (infants and children) **aPAD**= acute RfD / FQPA SF = 0.017 mg/kg/day (infants and children) = 0.17 (general population)	Single Dose Rat Study (Nakai et al. 1992) LOAEL= 50 mg/kg/day based on adverse testicular effects including sloughing (premature release) of immature germ cells 2 days post exposure, atrophy of a few seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter, and slight abnormal growth of the efferent ductules at 70 days post exposure.
Chronic Dietary	NOAEL=2.5 mg/kg/day UF = 100 **Chronic RfD=** 0.025 mg/kg/day	FQPA SF = 10 (children and females 13-50 yrs) **cPAD**= chronic RfD / FQPA SF = 0.0025 mg/kg/day (children and females) = 0.025 (general population)	2 year dog study with MBC LOAEL= 12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes.
Short-and Intermediate Term Dermal (a)	Oral NOAEL =10 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams

Table 4 Summary of Doses and Toxicological Endpoints for MBC			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF* and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Long-Term Dermal (a)	Oral NOAEL =2.5 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	2 year dog study with MBC LOAEL= 12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs.
Short-, Intermediate- and Long Term Inhalation	Inhalation NOAEL= 0.96 (10 mg/m^3)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	90 day rat inhalation study with benomyl LOAEL= 4.8 mg/kg/day (50 mg/m^3)based on Olfactory degeneration in the nasal cavity
Cancer	Q1* = $2.39x10^{-3}$ $(mg/kg/day)^{-1}$	Q1* = $2.39x10^{-3}$ $(mg/kg/day)^{-1}$	2 year mouse study with MBC based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.
UF = Uncertainty Factor
PAD = Population Adjusted Dose (includes UF and FQPA safety factor)
LOC= Level of Concern
MOE = Margin of Exposure
(a) Since an oral value was selected, 3.5% dermal absorption factor should be used for route-to-route extrapolation.

3.3.3 Relative Potency Factors

In this assessment, risk estimates for benomyl and MBC and other metabolites of concern were added together to account for total risk estimates for target organs of concern. This is considered appropriate because both chemicals have aPADs that are based on the same effects (i.e., developmental effects for the aPADs for females, testicular effects for the aPADs for all other populations, and the liver is a target organ of chronic exposure) and because individuals may consume both benomyl and MBC residues simultaneously on a given food commodity since benomyl rapidly degrades to MBC. A relative potency factor (RPF) approach was used to sum risk estimates from benomyl and MBC as MBC equivalents consistent with USEPA (1999) guidance. Using the RPF approach, all benomyl dietary exposure estimates were adjusted downwards to account for differences in aPADs and cPADs between benomyl and MBC. The RPFs used in this assessment are shown on Table 5 below.

Table 5 Relative Potency Factors (RPFs) Used to Convert Benomyl Exposures into MBC Equivalents			
Toxicological Endpoint	**Benomyl (mg/kg/day)**	**MBC (mg/kg/day)**	**Relative Potency Factor (a)**
Acute PAD, females (13-50 years)	0.03	0.01	0.33
Acute PAD, infants and children	0.025	0.017	0.68
Acute PAD, general population	0.25	0.17	0.68
Chronic PAD, females, infants and children	0.013	0.0025	0.192
Chronic PAD, general population	0.13	0.025	0.192

(a) MBC PAD divided by Benomyl PAD.

3.4 Endocrine Disrupter Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, benomyl and MBC may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Uses

Benomyl is a benzimidazole carbamate and systemic foliar fungicide registered to control a wide range of diseases of fruits, nuts, vegetables, and field crops. Benomyl is manufactured in the United States by E.I. du Pont de Nemours & Company and is sold under the trade name of Benlate®. Benomyl is formulated as a wettable powder (WP) and wettable powder in water

soluble film (i.e., packets, WSP), both of which contain 50 percent active ingredient. These formulations may be applied as delayed dormant, foliar, seed, and seed piece treatments. There are approximately 83 tolerances for food and/or feed commodities such as citrus, vegetable crops, oats, wheat and rice, etc. Benomyl is not registered for residential use.

The following uses are being supported by DuPont: almonds, apples, anise, apricots, asparagus, avocado, banana, barley, bean vine, blueberries, brassica (broccoli, brussels sprouts, cabbage, chicory, chinese cabbage, cauliflower, collards, kale, kohlrabi, mustard greens, rutabagas, and turnips), caneberries (raspberries, blackberries, boysenberries, loganberries, and dewberries), cardoon, carrots, celery, cherries, citrus, conifers, corn, cucurbits (cucumber, melons, pumpkins, and squash), currants, dandelions, dill, figs, grapes, macadamia nuts, mangoes, mushrooms, nectarines, onions, oats, papayas, peaches, peanuts, pears, peas, pecans, peppers, pineapple, pistachio, plums, prunes, rape, rice, rye, soybeans, spinach, strawberry, sugar beets, tomatoes, wheat, and yams.

Recently canceled uses include post harvest use on apples, citrus, pineapple, bananas, pears, and stone fruit; flowers; ornamentals; bulbs; shade trees; greenhouse (hydroponic/chemigation uses); dip treatment for sugarcane; drench treatment for strawberry plants; and turf and residential lawns.

BEAD estimates that the annual total domestic usage of benomyl is approximately 1,000,000 lbs ai for over 1,500,000 acres treated. Benomyl has the largest agricultural market in terms of total pounds ai allocated to rice (27%), wine grapes (15%), soybeans (6%), almonds (5%), apples (4%), and peaches (3%). Most of the usage is in AR, LA, MS, NY, OK, TX, and WA. Crops with a high percentage of their total U.S. planted acres treated include squash (47%), raspberries (46%), celery (43%), brussel sprouts (38%), and nectarines (37%). Crops with less than one percent crop treated include asparagus, barley, dry beans, corn, cotton, lemons, green peas, pistachios, potatoes, sorghum, soybeans, sugar beets, sugar cane, sweet corn, walnuts, wheat, and woodland crops.

Comprehensive lists of benomyl end-use products (EPs) and of use patterns with food/feed uses which are subject to re-registration are summarized in the Revised Product and Residue Chapter (Memorandum from J. Morales to D. Smegal, February 7, 2001, D275445).

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Tolerances for residues of benomyl are currently expressed in terms of benomyl and its metabolites containing the benzimidazole moiety in/on plant, animal, and processed food/feed commodities. However, the HED Metabolism Committee recently recommended that the tolerance expression in 40 CFR §180.294(a) and (b) be modified to include residues of benomyl, carbendazim or MBC (methyl 2-benzimidazole carbamate), and 2-AB (2-amine-1-H-benzimidazole) in plant commodities, and benomyl, MBC, 5-HBC (methyl-5-hydroxybenzimidazole carbamate) and 4-HBC (methyl-4-hydroxybenzimidazole carbamate) in

animal commodities. There are two separate analytical methods that quantify the residues of concern in plant and animal commodities (i.e., one method for benomyl, MBC, and 2-AB in plant commodities, and one method for benomyl, MBC, 5-HBC and 4-HBC in animal commodities). The conclusions specified in the "Tolerance Reassessment Summary" section of the Revised Product and Residue Chemistry Chapter (Memorandum from J. Morales to D. Smegal, February 7, 2001, D275445) reflect this decision.

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for carbendazim (MBC) residues occurring as a metabolic product of benomyl in/on various plant and animal commodities (see *Guide to Codex Maximum Limits For Pesticide Residues, Part A.1, 1995*). The Codex MRLs and the U.S. tolerance are not compatible because the U.S. tolerance expression currently includes the parent compound benomyl and all metabolites containing the benzimidazole moiety, and will be modified to include residues of benomyl, MBC, 2-AB, 4 HBC and 5 HBC.

Plant Metabolism. The qualitative nature of the residue in plants is adequately understood based on studies with soybeans, rice, peaches, and sugar beets. The HED Metabolism Committee has determined that the residue to be regulated in plant commodities include benomyl, MBC, and 2-AB.

Animal Metabolism. The qualitative nature of the residue in animals is adequately understood based on acceptable ruminant and poultry metabolism studies. The HED Metabolism Committee concluded that 5-HBC and 4-HBC should be included in the benomyl dietary exposure analysis for animal commodities. The residue to be regulated in animal commodities include benomyl, MBC, 4-HBC, and 5-HBC.

Residue Analytical Methods - Plants and Animals.

Methods for determination of residues in/on plant commodities: Based on the revised tolerance expression, the current enforcement method is not acceptable for residues of concern in plant commodities because it does not detect 2-AB. However, the methods for enforcing the established tolerance are acceptable. The Pesticide Analytical Manual (PAM) Volume II lists colorimetric and fluorometric procedures (Methods I and A) and a GLC method using nitrogen selective and electron capture detection for analysis of residues of benomyl and its metabolite MBC in/on plant commodities. A HPLC method is listed (Method II) for analysis of residues of benomyl and its metabolites MBC, 4-HBC, and 5-HBC in/on plant commodities and in animal commodities. The method does not distinguish the residues for benomyl from its metabolites.

Method II does not describe the determination of metabolite 2-AB, which is a residue of concern in plant commodities as a result of the recent HED Metabolism Committee deliberations. The PAM method does not adequately recover 2-AB (radioactive) from soybeans. A revised residue method (the ethanol:detergent method) recovered 84% 2-AB from soybeans. This method should undergo an independent laboratory validation (soybeans and rice grain) and an Agency method try out for use as an enforcement method. The data collection methods for benomyl and its residues of concern are HPLC methods with UV detection in which benomyl is converted to carbendazim (MBC); the limit of quantitation for all listed commodities was 0.01 ppm. These methods are essentially identical to Method II in PAM Volume II.

Methods for determination of residues in/on animal commodities: Based on the revised tolerance expression, the current enforcement and data collection methods are acceptable for all residues of concern in animal commodities. PAM Volume II provides a HPLC method (Method II) for analysis of residues of benomyl and its metabolites MBC, 4-HBC, and 5-HBC in animal commodities. The data from the [^{14}C]MBC goat study indicate that a method that uses aluminum nickel catalysis (Raney nickel) and hydrolysis might be suitable for tolerance enforcement. The metabolism method for identifying liver residues was similar to Method II in PAM II other than the Raney nickel step. HED believes that the current PAM II animal method can readily be modified to satisfy as an enforcement method (and residue method) for benomyl residues in liver.

Multiresidue methods: The FDA PESTDATA database dated 1/94 (PAM Volume I, Appendix I) indicates that benomyl is completely recovered (>80%) using multiresidue method Section 302 (Luke method; Protocol D). Benomyl and carbendazim (MBC) are completely recovered using Section 404; no data are available for 2-AB, 4-HBC, and 5-HBC. These data are required.

Storage Stability. Storage stability studies have been submitted demonstrating that residues of MBC are stable for up to 3 years of frozen storage in/on wheat and wheat straw. To completely support the storage intervals and conditions of the samples from the snap bean residue reduction study, storage stability data for 2-AB are required. The requirements for storage stability data are not considered fulfilled for reregistration purposes. Storage stability data are still required to support established tolerances.

Storage stability data are required to support the recently submitted data on carrots. Information on sample storage intervals and conditions are still required for peanuts. The registrant should recognize that residue studies that are incomplete with respect to sample handling and storage information may have to be repeated.

The registrant should also submit storage stability data for 4-HBC, and 5-HBC in animal commodities.

Magnitude of the Residue in Plants. The reregistration requirements for magnitude of the residue data have been satisfied for the following commodities: almond hulls; apples; avocados; bananas; barley, grain and straw; beans, succulent and dry; blackberries; blueberries; boysenberries; broccoli; cabbage; cauliflower; celery; cherries, citrus fruits; cucumbers; currants; dandelions; dewberries; garlic; grain dust; grapes; kohlrabi; loganberries; mangoes; melons; mushrooms; nuts (almonds, macadamia nut and pecans); oats, grain and straw; papayas; peaches; peanuts; peanut hay; pears; pineapples; pistachios; plums; pumpkins; raspberries; rice, grain and straw; rutabagas; rye, grain and straw; soybeans; squash, summer and winter; strawberries; sugar beet, sweet potatoes, root and tops; tomatoes; turnip, root and tops; yams, and wheat, grain and straw.

Additional residue data are required for apricots, nectarines, canola, carrots, corn (sweet), collards, mustard greens, rice, and spinach.

Because the grazing restrictions for barley, oats, rye, and wheat must be removed from EP labels, tolerances are required for barley forage, oat forage, rye forage, and wheat forage. The proposed tolerances must be supported by appropriate residue data.

HED is aware of mushroom data that might support a lower tolerance on this commodity, however this data has not been formally submitted to the Agency. HED will determine the adequacy of the mushroom residue data once it has been formally submitted for review.

Magnitude of the Residue in Processed Food/Feed. The reregistration requirements for magnitude of the residue in the processed commodities of oranges, pineapple, plums (fresh prunes), rice, soybeans, sugar beets, and tomatoes are fulfilled. Processing studies with peanuts were not required, as residues in peanuts were uniformly nondetectable (<0.1 ppm).

The established tolerances for dried apple pomace, dried grape pomace, and raisin waste should be revoked because the Agency no longer considers these to be significant livestock feed items.

Based on an apple processing study and new residue data submitted for this Raw Agricultural Commodity (RAC), a tolerance of 10 ppm should be proposed for wet apple pomace.

Residues concentrate in citrus oil. Based on a highest average field trial (HAFT) residue value of 1.2 ppm for citrus (preharvest) and a concentration factor of 1.4x from a single processing study, residues of 1.7 ppm could be expected in citrus oil. Since the reassessed citrus tolerance is 2.0 ppm, a separate tolerance for citrus oil is not required.

Data are available indicating that benomyl residues concentrate in soybean hulls (2x). Multiplication of this concentration factor by the HAFT from field trials (0.08 ppm) gives a value of 0.16 ppm for soybean hulls. A tolerance of 0.16 ppm should be proposed for soybean hulls.

An adequate processing study is available indicating that residues do not concentrate in commodities derived from tomatoes.

Magnitude of the Residue in Meat, Milk, Poultry, and Eggs. Adequate livestock feeding studies are available reflecting feeding levels up to 50 ppm for cattle and 25 ppm for poultry. Given the reassessed tolerance levels, the maximum dietary burden for cattle would be approximately 22 ppm based on a diet of 50% barley/oat/wheat grain, 20% wet apple pomace, 20% sugar beet leaves, and 10% wheat straw. The maximum dietary intake for poultry would be 0.2 ppm based on a cereal grain diet. The available data support the established tolerances.

Confined/Field Rotational Crops. The Environmental Fate and Groundwater Branch (EFGWB) reviewed the confined rotational crop study and determined that it was adequate (memo of Nelson 11/15/90). The following statement should appear on all benomyl EPs: "Do not rotate to crops other than those that appear on this label." The absence of a rotational crop restriction as above on the labels will result in a requirement for limited and/or full field rotational crop residue studies.

Reduction of Residue. Data depicting residue decline are available. These studies include common practices such as special processing and cooking studies that could reduce dietary estimated exposure to benomyl. A summary of benomyl residue reduction is presented below.

Apples: The commercial packing procedures (including water or detergent washing, brushing, waxing, and drying) reduced residue levels in/on apples to 0.8x of initial levels. Although consumer preparation, including washing and slicing apples, did not significantly affect the levels

of benomyl/MBC, peeling reduced residue levels to 0.6x of initial levels; residue levels in peeled, cooked apples were reduced to 0.3x of initial levels. However, to completely define the potential for reduction of benomyl residues of concern in/on apples during commercial packing and consumer preparation, residue data need to include 2-AB. No reduction factors were used because the individual food forms were not assessed.

Snap beans: The consumer preparation (including washing, boiling, and stir-frying) did not significantly affect the levels of benomyl/MBC residues in/on snap beans; commercial packing procedures (including sorting, washing, and hydro-cooling) reduced residue levels to 0.5-0.7x of initial levels. However, to completely define the potential for reduction of benomyl residues of concern in/on snap beans during commercial packing and consumer preparation, residue data need to include 2-AB.

The commercial processing procedures (washing, blanching, canning/cooking) significantly reduced the levels of benomyl/MBC residues in/on snap beans. Washing with water reduced residues to 0.2-0.5x of initial levels. Blanching reduced residues to 0.1-0.4x of initial levels and canning and cooking reduced residues to 0.03-0.2x of initial levels. However, to completely define the potential for reduction of benomyl residues of concern in/on snap beans during commercial processing, residue data need to include 2-AB. No reduction factors were used because the individual food forms were not assessed.

Peaches: Washing reduced benomyl/MBC residues in peaches to 0.26x the initial level and after peeling residues were 0.07x. After processing, residues in baby food peaches, canned peaches and baked peaches were 0.11, 0.01, and 0.004x the initial concentration. Since 2-AB was not detected in the peach metabolism study, residue data need not include 2-AB. No reduction factors were used because the individual food forms were not assessed.

4.2.2 Food Exposure

As noted previously, benomyl is registered for use on a wide variety of food crops, and has approximately 83 tolerances for food and/or feed commodities. Tolerances for residues of benomyl are currently expressed in terms of benomyl and its metabolites containing the benzimidazole moiety in/on plant, animal, and processed food/feed commodities which are MBC, 2-AB, 5-HBC and 4-HBC. However, the HED Metabolism Committee recently recommended that the tolerance expression in 40 CFR §180.294(a) and (b) be modified to include residues of benomyl, MBC and 2-AB in plant commodities and benomyl, MBC, 5-HBC, and 4-HBC in animal commodities. The tolerances published for benomyl have been reassessed (HED Revised Product and Residue Chemistry Chapter, memorandum from J. Morales to D. Fuller February 7, 2001, D275445). MBC and 2-AB are the only metabolites present in plant commodities, while only MBC, 5-HBC and 4-HBC are present in animal commodities. There are two separate analytical methods that quantify the residues of concern in plant and animal commodities.

Plant commodity tolerances range from 0.2 ppm to 50 ppm (bean vine forage). Animal commodity tolerances range from 0.1 ppm (milk, eggs, and fat, meat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep) to 0.2 ppm (liver of poultry). Adequate methods are available for the enforcement of established tolerances, as currently defined.

The refined Tier 3 acute and chronic dietary exposure assessments were conducted using version 6.77 of the Dietary Exposure and Evaluation Model (DEEM™) system. DEEM™ , developed by Novigen Sciences, Inc., calculates acute and chronic dietary exposure estimates to residues in food for the U.S. general population and various population subgroups. The software contains food consumption data from the USDA Continuing Survey of Food Intake by Individuals (CFSII) from 1989-1992. For chronic dietary risk assessments, the 3-day average of the consumption data for each sub-population is combined with average residues in commodities to determine the average exposure in mg/kg/day. For acute dietary risk assessment, the entire distribution of single day food consumption events is combined with a distribution of residues (probabilistic analysis, referred to as "Monte Carlo") to obtain a distribution of exposures in mg/kg/day.

Dietary assessments were separately performed for benomyl and the sum of the metabolites of MBC and other regulated metabolites. Assessments were performed for acute, and noncancer and cancer chronic exposures. For commodities evaluated based on PDP data, an adjustment factor (calculated from metabolism studies) in DEEM was used to apportion the residue values to either benomyl or to MBC + other metabolites. For commodities assessed based on field trial data, actual residue data for benomyl and the individual metabolites (i.e., MBC and 2-AB) were used to estimate exposures. For animal commodities residues for the individual compounds of concern (i.e., benomyl, MBC, 4-HBC, and 5-HBC) were available.

For benomyl and MBC + 2-AB, inputs to the DEEM analysis include U.S. Department of Agriculture's (USDA's) Pesticide Data Program (PDP) monitoring data (1994-1998), and field trial residue data, submitted primarily by the registrant and percent crop treated data (BEAD Quantitative Usage Analysis for benomyl dated 3/2/99, and 9/2/99). Anticipated residues (ARs) used in dietary risk assessment are calculated based primarily on these two data sources with PDP data preferred over field trial data. The statistical design of the PDP program is specific for dietary risk assessment (i.e., sampling is done at wholesale distribution points instead of directly from the field) and the foods are prepared reflecting typical consumer practices (i.e., washing and peeling). Field trial residue data are considered by the Agency as an upper-end, or worst case scenario of possible residues, and are more suited to the requirements of tolerance setting than to the requirements of dietary risk assessment. Where percent crop treated estimates indicated no benomyl use, a default minimum assumption of 1% crop treated was applied. Where residues were nondetectable, one-half the limit of detection (LOD) was assumed for treated commodities. All available processing factors were incorporated into the dietary exposure analysis.

The Food and Drug Administration (FDA) Surveillance Monitoring Program data (1992-1995 and 1998) has limited data for benomyl that is insufficient for risk assessment purposes (i.e., there were only a few samples for a few commodities). Although this testing is limited, FDA found residues on green beans, peaches and apples, and on cherries, grapes and various berries: strawberries, blueberries, blackberries and raspberries.

PDP data are available for apples, oranges, peaches, grapes, bananas, tomatoes, broccoli, carrots, spinach, succulent fresh green beans, canned green beans, sweet corn, milk, and orange, apple juice, strawberries and cantaloupes. Of the 17 commodities monitored by PDP, strawberries, fresh green beans and peaches had the highest residues detected at the greatest frequency. Benomyl residues were detected at concentrations up to 4 ppm in 28% of strawberries (tolerance = 5 ppm), up to 1.6 ppm (tolerance = 2 ppm) in 13% of fresh green beans and up to 2.6 ppm

(tolerance = 15 ppm) in 17% of peaches. PDP detected no detectable residues or nearly no residues in milk, orange juice, oranges bananas, broccoli, cantaloupes, sweet corn, carrots, and spinach. Milk PDP data were not used in the assessment because of the high limit of detection (LOD), and therefore data from a feeding/metabolism study were used. There were residues on 3% of grapes, up to 0.8 ppm (tolerance = 10 ppm). There were residues on 10% of apples, up to 0.35 ppm (tolerance = 7 ppm) and in 1.5 % of apple juice up to 0.27 ppm. For tomatoes, 2% had residues up to 0.24 ppm (tolerance = 5 ppm).

PDP data from17 commodities were translated and used to assess exposure from approximately 82 commodities. For example, PDP data for oranges were translated to other citrus crops including grapefruit, lemons, limes, tangerines, and tangelos. PDP apple data were translated to pears, while PDP peach data were translated to stone fruit (apricots, nectarines, plums, etc). PDP cantaloupe data were translated to melons, winter squash, and pumpkins, while PDP broccoli data were translated to collards, cauliflower and cabbage.

Surrogate field trial data from similar crops were used, if necessary, to assess crops without field trial data. Examples include: blackberry or blueberry data were used as a surrogate to assess all berries, while almond data were used to assess all tree nuts. Field trial data were used to assess wine exposure. While PDP table grape data are available to assess wine grapes, these data were not used because BEAD indicates that wine grapes are more extensively treated with benomyl than table grapes.

Benomyl residues may be either concentrated or reduced by activities such as drying (dried fruits), processing (juice, catsup, etc.), washing, peeling and cooking. Acceptable processing studies were available and incorporated into this assessment for raisins and grape juice from grapes, prunes and prune juice from plums, orange peel, soybean oil, processed tomato products and processed rice. DEEM default factors were used for all other processed commodities. These processing factors are used together with the anticipated residue estimates in or on the associated RAC to estimate the residue in various processed fractions.

HED expresses dietary risk estimates as a percentage of the acute and chronic population adjusted dose (PAD). The PAD is the adjusted RfD reflecting the retention or reduction of the FQPA safety factor for all populations. The PAD is the Reference Dose (RfD), which is derived from an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control, along with the application of uncertainty factors. The percent of the PAD is calculated as the ratio of the exposure value to the PAD (exposure/PAD x 100 = % PAD). As shown on Table 6, for benomyl there are three population adjusted doses pertaining to acute dietary exposure and two PADs for chronic exposure. There are also three population adjusted doses pertaining to acute dietary exposure and two PADs for chronic exposure, as shown on Table 7. Exposures less than 100% of the PAD do not exceed HED's level of concern. For this analysis, it was assumed that the metabolites 2-AB, 5-HBC and 4-HBC have the same toxicity as MBC.

In addition, cancer risks were estimated using a cancer unit risk estimate of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for both benomyl and MBC + other metabolites. Cancer risks are calculated by multiplying the 70 year exposure estimate for the U.S. population by the Q_1^*, and are expressed as a probability of developing cancer. As noted previously, benomyl dietary exposure was

adjusted to MBC equivalents by multiplying by a factor of 0.66, which is the ratio of MBC and benomyl molecular weights (190:290). This adjustment is based on the Ad Hoc CARC decision (memo from D. Smegal to D. Fuller, September 21, 2000, D269149).

4.2.2.1 Acute Dietary

A highly refined, Tier 3 acute probabilistic dietary exposure analysis was conducted for benomyl, incorporating maximum percent crop treated estimates from the Biological and Economic Analysis Division (BEAD), PDP monitoring data, and field trial data. Because monitoring data usually are derived from samples that are composites of multiple units of produce, such samples were "decomposited" for the purpose of estimating single serving acute exposure. The details of the dietary analysis are presented in memo from J. Morales/D. Soderberg to D. Smegal/D. Fuller, October 11, 2000. D268933.

Exposure (consumption x residues) was compared to the appropriate acute population adjusted dose shown previously on Tables 3 and 4 and listed in the footnotes of Table 6. As noted previously, there are a total of six aPADs, three each for benomyl and MBC. The aPADs differ based on toxicological endpoint of concern (i.e., developmental effects for females, testicular effects for all other populations) and application of the 10X FQPA factor (i.e., only applied to females 13-50 yrs and children subgroups). The acute dietary risk analysis estimates the distribution of single day exposures for the overall U.S. population and certain subgroups. The analysis evaluates exposure to the chemical for each food commodity.

Table 6 summarizes the acute probabilistic dietary risk estimates for the U.S. Population and the most highly exposed sub-populations. For the U.S. population and all other sub-populations, HED's exposure estimates at the 99.9th percentile for both benomyl and MBC + other metabolites were less than 100% of the aPAD, and therefore these risk estimates do not exceed HED's level of concern. Infants <1 year had the highest risk estimates for benomyl, while females (13-50 years) had the highest risk estimates for MBC. While MBC dietary exposure is higher for children, the aPAD for females is lower than the aPAD for children, resulting in a higher risk estimate. Dietary exposure to infants <1 year represents 14.8% and 45.5% of the aPAD for benomyl and MBC + other metabolites, respectively. Dietary exposure to females (13-50 years) represents 6.48% and 76.4% of the benomyl and MBC+ other metabolites aPADs, respectively.

In addition, risk estimates for benomyl and MBC +other regulated metabolites were added together to account for total risk estimates for the target organs of toxic concern. This is considered appropriate because both chemicals have aPADs that are based on the same toxic effects (i.e., developmental effects for females, and testicular effects for all other population groups), and because individuals may consume both residues simultaneously on a given food commodity. A relative potency factor (RPF) approach was used to sum dietary risk estimates from benomyl and MBC as MBC equivalents consistent with USEPA guidance (USEPA 1999). Using the RPF approach, all benomyl dietary exposure estimates were adjusted downwards to account for the differences in aPADs between benomyl and MBC (i.e., general population aPAD is 0.25 mg/kg/day for benomyl, but 0.17 mg/kg/day for MBC, therefore a factor of 0.68 was applied to the benomyl dietary estimate). As shown on Table 6, this approach is identical to summing the %aPADs for benomyl and the %aPAD for MBC. The total dietary risk estimates for benomyl and MBC, by target organ, are also below HED's level of concern for all population

groups. The highest total dietary risk estimate represents 83% of the aPAD for females of child bearing age (13-50 years) based on developmental effects.

Table 6. Summary of Benomyl/MBC Acute Dietary Probabilistic Exposure Analysis (Tier 3) by DEEM (99.9th Percentile).

Population (a)	Benomyl Estimate		MBC+other metabolites Estimate (from Benomyl)		Benomyl and MBC	Total Risk Estimate for Benomyl and MBC
	Exposure (mg/kg/day) (b)	% aPAD (c)	Exposure (mg/kg/day) (b)	% aPAD (c)	Total Exposure in MBC Equivalents (mg/kg/day) (d)	% aPAD (e)
U.S. Population	0.002237	0.89	0.007194	4.2	0.008715	5.1
All Infants <1 year	0.003703	14.8	0.007735	45.5	0.01025	60
Children 1-6 years	0.003680	14.7	0.008604	50.6	0.0111	65
Children 7-12 years	0.002940	11.8	0.006208	36.5	0.0082	48
Females 13-50 years	0.001945	6.48	0.007637	76.4	0.00827	83
Males 20+ years	0.00179	0.72	0.006951	4	0.00817	4.7

(a) In addition to the U.S. population -all seasons, the most highly exposed subgroup within each of the infants, children, females, and males groups is listed.

(b) 99.9th percentile exposure.

(c) Percent of aPAD = (Exposure ÷ aPAD) x 100%. aPAD for the general population = 0.25 and 0.17 mg/kg/day for benomyl and MBC, respectively, aPAD for females (13-50 years) = 0.03 and 0.01 mg/kg/day for benomyl and MBC, respectively and aPAD for children subgroups = 0.025 and 0.017 mg/kg/day for benomyl and MBC, respectively.

(d) Sum of benomyl and MBC dietary exposures, where benomyl dietary exposure adjusted using the relative potency factors (RPFs) of 0.68 for all populations and 0.33 for females to account for the differences in the aPADs for benomyl and MBC. Example, for females 13-50 yrs benomyl exposure = 0.001945 mg/kg/day * 0.33 = 0.00064 mg/kg/day in MBC equivalents, where 0.00064 mg/kg/day + 0.007637 mg/kg/day = 0.00827 mg/kg/day.

(e) Percent of MBC aPAD = (Total exposure in MBC equivalents ÷ aPAD for MBC) x 100%. This is also equivalent to: %aPAD from benomyl + %aPAD from MBC. This is considered appropriate because the aPAD are based on the same effects for each population (i.e., testicular effects for all populations except females, where developmental effects were observed).

The uncertainties in the acute dietary exposure estimates are discussed below following the chronic dietary exposure assessment discussion.

4.2.2.2 Chronic Cancer and Non-Cancer Dietary

A refined Tier 3 chronic exposure analysis was performed using the DEEM ™ exposure modeling software. The input values for the Tier 3 analyses included the PDP in addition to average residues from field trials and incorporated average percent of the crop treated information from BEAD. As noted previously, there are two chronic population adjusted doses (cPADs) each for both benomyl and MBC. These cPADs were presented previously on Tables 3 and 4, and are shown in the footnotes of Table 7. Exposure (consumption) was compared to the relevant cPAD

for each chemical and subpopulation. A summary of the residue information included in this analysis and details of the dietary analysis are presented in memo from J. Morales/D. Soderberg to D. Smegal/D. Fuller, October 11, 2000. D268933.

As shown in Table 7, non-cancer chronic risk estimates for all population subgroups are below the Agency's level of concern (<100% cPAD). Children (1-6 years) are the highest exposed population subgroup for both benomyl and MBC +other metabolites at 0.6% and 6.7% of the cPADs, respectively. Similar to the acute dietary risks, a total dietary risk estimate was calculated, because of similar adverse effects, and the potential for simultaneous exposure to these chemicals on food commodities. A RPF approach was used to sum dietary risk estimates from benomyl and MBC as MBC equivalents. Using the RPF approach, all benomyl dietary exposure estimates were adjusted downwards to account for the differences in cPADs between benomyl and MBC (i.e., general population cPAD is 0.13 mg/kg/day for benomyl, but 0.025 mg/kg/day for MBC, therefore a factor of 0.192 was applied to the benomyl dietary estimate). As shown on Table 7, this approach is identical to summing the %cPADs for benomyl and the %cPAD for MBC. As shown on Table 7, the highest total dietary risk estimate of 7.2% for children 1-6 years, was also well below the cPADs, and therefore, does not exceed HED's level of concern.

Table 7 also presents the lifetime (70 year) cancer risk estimates for the U.S. general population. The cancer risk estimates are 6.7×10^{-8} and 2.3×10^{-7} for benomyl and MBC, respectively. The total dietary cancer risk estimate is 3×10^{-7}. These lifetime risk estimates are below the level the Agency generally considers to be negligible for excess lifetime cancer risk (i.e., 1×10^{-6}). It is appropriate to add the cancer risk estimates from benomyl and MBC because both chemicals cause mouse liver tumors, and the Q_1^* for MBC has been applied to benomyl, although benomyl exposure was adjusted downward by a factor of 0.66 to account for the difference in molecular weight between MBC and benomyl.

Uncertainties of Dietary Exposure Estimates

The Agency believes that the Tier 3 risk assessment presented is the most refined to date for acute dietary exposure to benomyl and MBC. However, there are some uncertainties associated with this exposure estimate as follows.

(a) The consumption database used in the dietary exposure analysis (CSFII, 1989-1992) has a limited number of individuals in the age group infants less than one year old. The USDA is currently conducting the Supplemental Children's Survey (approximately 5000 children).

(b) The dietary exposure analyses relied primarily on monitoring data obtained from regional distribution warehouses for PDP data. Residues potentially present on items purchased at roadside produce stands or farmer's markets are not represented in this analyses.

(c) Relative amounts of benomyl and MBC were determined from plant metabolism studies. Because benomyl degrades to MBC, over time more MBC and less benomyl may be present in food at the time of consumption. In addition, for the acute dietary assessment, it may be conservative to add the 99.9th exposure estimates for benomyl and MBC,

because as benomyl residues decline, MBC residues increase. Consequently, individuals could be exposed to high-end (i.e., 99.9th) residues of either benomyl or MBC, not both at the same time.

(d) Pesticide concentrations used in this assessment could be further reduced by washing and peeling commodities (except for those commodities for which PDP data are available).

(e) No cooking factors could be incorporated in this dietary exposure analysis. If DuPont has any such data they should be supplied to the Agency. If reduction of residues is noted upon cooking, this could lead to lower acute dietary exposure estimates.

(f) In the absence of adequate toxicity data for the metabolites 5-hydroxy-2-binzimidazolecarbamic acid, methyl ester (5-HBC), 4-HBC and 2-aminobenzimidazole (2-AB), it was assumed that all three metabolites are toxicologically equivalent to MBC on a gram basis. Additional toxicological data have been requested to support this assumption.

(g) Data from four plant metabolism studies were used to extrapolate to all other registered plant uses to estimate the ratio of benomyl:MBC residues.

(h) Wine is a significant contributor to the adult population sub-groups exposure. Although there is monitoring data available for table grapes from PDP, wine was evaluated in the current assessment using wine grape field trial results because data from the BEAD indicate that wine grapes are more extensively treated with benomyl than are table grapes. However, the labeled application rates are identical for table grapes and wine grapes. A vinification study is not available.

(i) Mushrooms were the most important contributor to chronic exposure estimates to benomyl for children 1-6. Since no percent crop treated estimates are available from BEAD for mushrooms, they were estimated using 100% crop treated. Quantitative usage information on mushrooms could help refine the risk. HED is aware of new mushroom data that could potentially support a lower tolerance for this commodity. However, this data has not yet been formally submitted to the Agency, and will be reviewed upon receipt.

(g) Strawberries were the second most important contributor to exposure estimates for children 1-6, and blueberries, peaches, beans and pome fruits in general had a similar contribution to dietary exposure estimates. The field trial residues in berries were relatively high. High residues on berries, however, are supported by the limited FDA monitoring data for berries and also by several samples analyzed in the FDA Total Diet Study. Thus while market basket data on berries would certainly help refine the risk estimate, it might have a relatively small effect upon the size of the exposure estimates. Data for peaches, beans and pome fruits were all well refined.

Table 7
Summary of Benomyl and MBC Tier 3 Chronic Dietary Exposure Analysis by DEEM

Population Subgroup (a)	Benomyl			MBC +other metabolites (from benomyl)			Benomyl and MBC	Total Risk for Benomyl and MBC	
	Exposure (mg/kg BW/day)	%cPAD (b)	Lifetime Cancer Risk Estimate (d)	Exposure (mg/kg BW/day)	%cPAD (b)	Lifetime Cancer Risk Estimate (d)	Total Exposure in MBC Equivalents (mg/kg/day) (e)	%cPAD (c)	Lifetime Cancer Risk Estimate (f)
US Population	0.000042 (Noncancer) 0.000028 (g) (cancer)	0.03	$6.7x10^{-8}$	0.000091	0.36	$2.3x10^{-7}$	0.000099 (noncancer) 0.000124 (cancer)	0.4	$3x10^{-7}$
All infants (< 1 yr)	0.000045	0.3	NA	0.000096	3.8	NA	0.0001046	4.2	NA
Children (1-6 years)	0.000072	0.6	NA	0.000167	6.7	NA	0.00018	7.2	NA
Children (7-12 years)	0.000047	0.4	NA	0.000107	4.3	NA	0.00016	4.6	NA
Females 13-50 years	0.000040	0.3	NA	0.00009	3.6	NA	0.000098	3.9	NA
Males 20+ years	0.000038	0.03	NA	0.000089	0.34	NA	0.0000963	0.37	NA

NA = Not applicable, these groups are included in the 70 year U.S. population estimate

(a) U.S. population -all seasons, and the most highly exposed subgroup within each of the infants, children, females, and males groups is listed.

(b) Percent of cPAD=(Exposure÷cPAD)x100%. cPAD for the general population = 0.13 and 0.025 mg/kg/day, cPAD for females (13-50) = 0.013 and 0.0025 mg/kg/day and cPAD for children subgroups = 0.013 and 0.0025 mg/kg/day for benomyl and MBC, respectively.

(c) Percent of MBC cPAD = (Total exposure in MBC equivalents ÷ cPAD for MBC) x 100%. This is also equivalent to the sum of the %cPAD for benomyl and MBC+2-AB. This is considered appropriate because the cPADs are based on the same adverse effect for benomyl and MBC.

(d) Lifetime cancer risk = Exposure x Q1*.

(e) Sum of benomyl and MBC diet exposure, where benomyl dietary exposure adjusted using the relative potency factors (RPFs) of 0.192 for all populations to account for the differences in the cPADs for benomyl and MBC. Example, benomyl exposure = 0.000040 mg/kg/day * 0.192 = 0.0000077 mg/kg/day in MBC equivalents. RPF not used for cancer.

(f) Total lifetime cancer risk is the sum of benomyl and MBC cancer risks.

(g) Benomyl cancer dietary exposure multiplied by 0.66 to account for molecular weight differences between benomyl and MBC because Q1* is based on MBC tumor.

4.3 Drinking Water Exposure/Risk Pathway

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a quantitative drinking water exposure analysis and risk assessment for benomyl and MBC. Therefore, the Agency is presently relying on water quality models to estimate environmental concentrations (EECs) of pesticides in ground and surface water to estimate drinking water exposures to benomyl and MBC. Generic Estimated Environmental Concentrations (GENEEC) and/or the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) (both product estimates of pesticide concentration in a farm pond) predict EECs for pesticides in surface water. The Screening Concentration in Ground Water (SCI-GROW) (an empirical model based on actual monitoring data collected for a number of pesticides that serve as benchmarks) predicts EECs for pesticides in ground water. These models take into account the use patterns and environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water may have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for assessing whether a pesticide is likely to be present in drinking water at concentrations that would exceed human health levels of concern.

The SCI-GROW model generates a single EEC value of pesticide concentrations in ground water. That EEC is used to assess drinking water exposures in assessments of both acute and chronic dietary risk. It is not unusual for the ground water EEC to be significantly lower than the surface water EECs. The GENEEC model generates several time-based EEC values of pesticide concentration in surface water, ranging from 0-days (peak) to 56-days (average). The GENEEC peak EEC is used in assessments of acute dietary risk; the GENEEC 56-day (average) EEC is used in assessments of chronic (non-cancer and cancer) dietary risk. PRZM/EXAMS provides longer duration values (up to a 36-year mean) of pesticide concentrations in surface water, and is mainly used when a refined EEC is needed.

4.3.1 Environmental Profile

The Environmental Fate and Effects Division (EFED) conducted a drinking water assessment for benomyl and its primary degradate, MBC, based on an analysis of existing ground and surface water monitoring data in conjunction with Tier 1 modeling (using GENEEC and SCI-GROW) (Attached memos from R. Pisigan dated November 29, 2000, J. Peckenpaugh dated January 14, 1998 and May 4, 1999).

The available environmental fate data suggest that benomyl rapidly degrades to MBC following application to agricultural crops. Benomyl and MBC have a low potential to leach to groundwater in measurable quantities from most typical agricultural uses based on their high soil organic carbon partition coefficients (Koc) of 500 L/kg and 2,100 L/kg, respectively. Although limited, the available data indicate that the primary metabolite of benomyl, MBC is less mobile, and significantly more persistent in many soils, especially under anaerobic conditions. The MBC aerobic soil half-life is 320 days, while the aerobic and anaerobic aquatic metabolism half-lives are 61 and 743 days, respectively. EFED notes that under usual hydrogeological conditions, benomyl will not persist long enough to reach surface or ground water, and thus most residues in

surface or ground water will consist of MBC. EFED also concludes that MBC will probably not reach ground water to any significant concentration due to its high Koc. EFED (EFED; memos by R. Pisigan dated November 29, 2000, J. Peckenpaugh dated January 14, 1998 and May 4, 1999) has provided a screening-level drinking water assessment using simulation models and an analysis of available monitoring data to estimate the potential concentrations of benomyl and MBC in ground and surface water.

4.3.2 Estimated Environmental Concentration (EECs)

EFED conducted screening-level assessments to generate EECs for benomyl and MBC using the simulation models SCI-GROW (Tier 1) for ground water and Tier I GENEEC for surface water. The modeling was conducted based on the environmental profile and the maximum seasonal application rate proposed for benomyl use on citrus: 1.5 lbs ai benomyl/acre with two treatments per year (i.e., 3 lb ai benomyl/acre/year). As noted previously, only MBC was evaluated in surface and ground water because benomyl rapidly degrades (within hours) to MBC. The GENEEC models indicate that MBC has the potential to pollute surface waters and consequently drinking waters, via dissolution in runoff water as well as adsorption to eroding soil, especially in areas with large amounts of annual rainfall that could result in large volumes of runoff.

EFED evaluated limited ground water monitoring data for benomyl from three states, Arkansas, Oregon and California (Pesticides in Ground Water Database, EPA 1992), in addition to two rice monitoring studies from Arkansas and Louisiana. However, EFED concluded that these data are inadequate for evaluating long-term annual benomyl or MBC concentrations due to short sampling interval, small number of samples, and small geographical distribution. Benomyl was not detected in Arkansas or Oregon, and MBC was not analyzed. In California, benomyl was detected in one well that was attributed from a point source of contamination. EFED concluded that the results of the rice monitoring studies conducted during the early 1990s are only useful for ecological risk assessments, because the samples were collected from low order surface water bodies, canal drainage and sloughs, which are not suitable for drinking water assessments. The EECs are shown on Table 8.

Table 8 EFED ESTIMATED ENVIRONMENTAL CONCENTRATION (EECs)

Chemical	Ground Water SCI-GROW (µg/L) (a)	Surface Water GENEEC (µg/L)	
		Acute	Chronic
Benomyl	Rapidly degrades to MBC within hours		
MBC	0.14 (acute and chronic)	15.8 (peak)	2.4 (7.2 divided by 3 based on HED policy)

(a) SCI-GROW (Screening Concentration in Ground Water) is an empirical model for predicting pesticide levels in ground water. The value from SCI-GROW is considered an upper bound concentration estimate.

EFED notes that there are significant uncertainties associated with the drinking water estimates which are as follows. The SCI-GROW screening model estimated benomyl groundwater concentrations for sandy soils with a shallow depth to ground water and therefore, represents a "worst case". As stated in the EFED memorandum (R. Pisigian, 11/29/00), the screening-level

model used to estimate the maximum concentrations of MBC in surface water (GENEEC) can substantially overestimate true drinking water concentrations. GENEEC assumes that the drinking water source is a 1 hectare pond with no mixing or dilution, that the entire watershed surrounding the pond is cropped and treated, and no treatment of the drinking water source. Therefore, these EECs are considered to be upper-bound, and it will be necessary to refine the GENEEC estimates.

4.4 Residential Exposure/Risk Pathway

All residential uses and landscape uses of benomyl have been canceled and are no longer supported by the registrant, DuPont. Therefore, no residential or non-occupational exposures are anticipated and a residential assessment is not required. There is potential for spray drift during aerial application, and at this time HED is developing guidance for characterizing exposures from this scenario. In addition, the Agency is developing guidance for characterizing exposures from other sources already not addressed such as from exposures to farm worker children.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require that for establishing a pesticide tolerance "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food, and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Aggregate risk assessments were conducted for: acute (1 day), short-term (1-7 days), intermediate-term (7 days to several months), and chronic (several months to lifetime) exposures to benomyl and MBC. The aggregate risk assessments for chronic exposures includes a non-cancer and a cancer assessment. In all, five aggregate risk assessments were conducted.

As part of each aggregate assessment, HED conducted aggregate assessments under two scenarios: (1) one that considered benomyl and MBC exposures resulting exclusively from benomyl uses and, (2) benomyl and MBC exposures from all uses, including benomyl and thiophanate-methyl uses, in addition to registered MBC uses. As noted previously, MBC is a common metabolite of both fungicides. These aggregate assessments are referred to as Aggregate 1 and Aggregate 2, respectively.

Aggregate 1 Assessment. Because benomyl and MBC have common toxicity endpoints (developmental effects for females of child bearing age, and testicular and liver effects for general population), it is appropriate to add benomyl and MBC dietary risk estimates. In addition, individuals may consume both residues simultaneously on a given food commodity. There are no residential or other non-occupational exposures to benomyl, or to MBC resulting from benomyl uses. Therefore, residential dermal and inhalation exposures are not anticipated to occur for the aggregate 1 assessment. Consequently, only oral aggregate exposures and risks from exposure to these compounds in food and water sources will be characterized for benomyl and MBC (resulting from benomyl uses).

Aggregate 2 Assessment. Thiophanate-methyl is registered for residential and recreational uses including lawn treatment, golf courses and home orchards. In addition, MBC is registered for tree injection and as a fungicide/preservative in paints, coatings, plaster and adhesives in residential settings. Consequently, residents could be exposed to registered MBC products via dermal and inhalation exposure during painting activities, and via inhalation to vapors in painted rooms. Residential exposures resulting from tree injection uses are considered to be negligible.

Therefore, the aggregate 2 assessment includes MBC exposures from all dietary (food and water) and residential/recreational uses. In addition, benomyl risk estimates were combined with the total MBC risk estimates because of common toxicity endpoints and simultaneous exposure on benomyl-treated commodities.

5.1 Acute Aggregate Risk

The acute aggregate risk estimate to benomyl and MBC addresses exposure from food and water. For the Tier III acute dietary exposure analysis, PDP monitoring data and field trial data, in conjunction with percent crop treated data were used to assess dietary exposures.

5.1.1 Aggregate 1: Benomyl and MBC (from Benomyl Use)

5.1.1.1 Aggregate Acute Risk Assessment

The benomyl acute dietary risk estimates range from 0.89% to 14.8% of the aPAD for benomyl, with infants < 1 year being the highest exposed population subgroup. For MBC, the acute dietary risk estimates range from 4.2% to 76.4%, with highest risk estimates for females (13-50 yrs). Thus, the acute dietary (food) risk estimate associated with benomyl or MBC exposure individually is below the Agency's level of concern.

Because benomyl and MBC have common acute toxicity endpoints (developmental effects for females, and testicular effects for general population), it is appropriate to add benomyl and MBC acute dietary risk estimates. In addition, individuals are likely to consume both residues simultaneously on a given food commodity. The highest total benomyl and MBC acute dietary risk estimate is 83% of the aPAD for developmental effects for females of child bearing age (13-50 years).

The acute aggregate assessment includes both dietary and drinking water exposures to benomyl and MBC. Drinking water monitoring data are not available, therefore, HED calculated drinking water level of comparisons (DWLOCs), which are discussed below to account for potential drinking water exposures to benomyl and MBC.

5.1.1.2 Acute DWLOC Calculations

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would result in risk estimates below HED's level of concern, when considering total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for a pesticide, the

DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW, GENEEC, PRZM/EXAMS). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

HED back-calculates DWLOCs by a two-step process: exposure [food + (if applicable) residential exposure] is subtracted from the PAD to obtain the maximum exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When EECs are **less** than DWLOCs, HED considers the aggregate risk [from food + water + (if applicable) residential exposures] to not exceed HED's level of concern.

DWLOCs based on simultaneous dietary exposure to both benomyl and MBC (as MBC equivalents) were estimated using the aPAD for MBC and by combining the 99.9th percentile dietary exposure for both chemicals. As noted previously, a RPF approach was used to convert the benomyl dietary exposure into MBC equivalents. Table 9 presents the total dietary exposure estimate as MBC equivalents.

The acute DWLOC values are also presented in Table 9. For each population subgroup listed, the acute PAD and the acute dietary (food) exposure (from Table 5) as MBC equivalents, for that subgroup were used to calculate the acute DWLOC for the subgroup, using the formulas in footnotes of Table 9.

Using conservative screening-level models, the acute estimated environmental concentrations (EECs) of MBC in groundwater (SCI-GROW) and surface water (GENEEC) are 0.14 µg/L and 15.8 µg/L, respectively. Because benomyl rapidly (within hours) degrades to MBC in water, EFED did not provide a groundwater or surface water EECs for benomyl. As shown on Table 9, the EFED EECs are below the DWLOCs for MBC (i.e., highest EEC of 15.8 µg/L is less than the lowest DWLOC of 52 µg/L for females 13-50 years). As noted previously, when EECs are **less** than DWLOCs, HED considers the aggregate risk [from food + water] do not exceed HED's level of concern. It should be noted that neither SCI-GROW or GENEEC models reflect concentrations after dilution (from source to treatment to tap) of drinking water treatment.

Table 9
Aggregate 1: DWLOCs for Acute Dietary Exposure
Benomyl and MBC (From Benomyl Use)

Population Subgroup (a)	MBC Acute PAD (mg/kg/day)	Acute Total Food Exposure as MBC Equivalents (mg/kg/day) (b)	Potential MBC Max. Water Exposure (mg/kg/day) c)	MBC Surface Water EEC GENEEC (µg/L)	MBC Ground Water EEC SCI-GROW (µg/L)	Acute DWLOC (µg/L) (d,e,f)
U.S. Population	0.17	0.008715	0.16	15.8	0.14	5,600
All Infants (< 1 Year)	0.017	0.01025	0.00675			68
Children (1-6 years)	0.017	0.0111	0.0059			59

Table 9 Aggregate 1: DWLOCs for Acute Dietary Exposure Benomyl and MBC (From Benomyl Use)						
Population Subgroup (a)	**MBC Acute PAD (mg/kg/day)**	**Acute Total Food Exposure as MBC Equivalents (mg/kg/day) (b)**	**Potential MBC Max. Water Exposure (mg/kg/day) c)**	**MBC Surface Water EEC GENEEC (µg/L)**	**MBC Ground Water EEC SCI-GROW (µg/L)**	**Acute DWLOC (µg/L) (d,e,f)**
Females (13-50 years)	0.01	0.00827	0.00173			52

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.

(b) 99.9th percentile exposure. Values are from Table 6, and are the sum of benomyl and MBC dietary exposure, reported as MBC equivalents. Benomyl exposure adjusted using the appropriate RPF to estimate MBC equivalents.

C) Maximum Water Exposure (mg/kg/day) = Acute PAD (mg/kg/day) - Acute Food.

(d) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/µg) x water consumed daily (L/day)].

(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.

(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

5.1.2 Aggregate 2: Benomyl and MBC from all Uses

HED also conducted an aggregate assessment of all MBC acute dietary exposure resulting from registered uses of both benomyl and thiophanate-methyl. As noted previously, MBC is a common metabolite of both fungicides. In addition, because benomyl and MBC have same toxic effects and target organs, the exposures for these chemicals were combined.

5.1.2.1 Aggregate Acute Risk Assessment

As shown on Table 10, the MBC acute dietary risk estimate from both benomyl and thiophanate-methyl uses exceeds HED's level of concern for infants (154% of aPAD), children 1-6 years (132% of aPAD), and females of child bearing age (13-50 years) (124% of aPAD) based on food exposure alone. In addition, dietary exposures from benomyl on the same food commodities would also contribute to the risk estimates for the specific target organs of concern (i.e., testicular effects and developmental effects), resulting in dietary exposures of even greater concern (i.e., up to 168% of the aPAD for infants). Therefore, any additional water exposure would only further contribute to risk estimates of concern. The highest EFED acute EECs for MBC in surface water are 15.8 µg/L based on benomyl use and 1,600 µg/L based on thiophante methyl use. Therefore, MBC water exposure could be significant, especially from thiophante methyl turf and ornamental uses. However, as stated in the EFED memorandum (R. Pisigian, 11/29/00), the screening-level model used to estimate the maximum concentrations of MBC in surface water (GENEEC) can substantially overestimate true drinking water concentrations. GENEEC assumes that the drinking water source is a 1 hectare pond with no mixing or dilution, that the entire watershed surrounding the pond is cropped and treated, and no treatment of the drinking water source. Therefore, these EECs are considered to be upper-bound, and it will be necessary to refine the GENEEC estimates.

This assessment is conservative, because benomyl and thiophanate-methyl are used on the same crops, and it is likely that a grower would use benomyl or thiophanate-methyl (and not both together) because both fungicides control similar pests. Consequently, it is more likely that individuals will be exposed to MBC and 2-AB from benomyl or thiophanate-methyl. For example, both fungicides are registered on some of the same crops including: almonds, apples, green and dry beans, bananas, squash, cucumbers, melons, peaches, plums, peanuts, soybeans, strawberries and wheat. In addition, although there are no PDP data for thiophanate-methyl, it is possible that the PDP data for benomyl include MBC and 2-AB environmental residues from thiophanate-methyl application. PDP data are available for five commodities (apples, bananas, green beans, peaches, and strawberries) that have both benomyl and thiophanate-methyl tolerances. The PDP data results, however are only for benomyl (and not for MBC). Because the PDP analytical method quantifies total benomyl, MBC and 2-AB residues from all sources (both benomyl and thiophanate-methyl), it is possible that the aggregate dietary MBC exposure and risk estimates (from benomyl and thiophanate-methyl use) may be overestimated to an unknown degree. BEAD estimates that the annual usage of benomyl is approximately two times greater than thiophanate-methyl.

5.1.2.2 Acute DWLOC Calculations

HED did not calculate acute DWLOCs because dietary exposure alone exceeds HED's level of concern for several population subgroups. Therefore, there is essentially no room in the risk cup for MBC drinking water exposure, and the DWLOCs are effectively zero.

Table 10
Summary of Acute Dietary Exposures and Risks
Probabilistic Exposure Analysis (Tier 3) by DEEM (99.9th Percentile)
Aggregate 2: MBC from All Uses (Benomyl and Thiophante Methyl)
(Excludes Water)

Population	Benomyl Estimate		MBC+other metabolites Estimate (from Benomyl)		MBC+other metabolites Estimate (from Thiophante Methyl)		Total Risk Estimate MBC Only	Total Risk Estimate for Benomyl and MBC
	Exposure (mg/kg/day)	% aPAD (a)	Exposure (mg/kg/day)	% aPAD (a)	Exposure (mg/kg/day)	% aPAD (a)	% aPAD (b)	% aPAD by target organ (c)
U.S. Population	0.002237	0.89	0.007194	4.2	0.006838	4	8.2	9
All Infants <1 year	0.003703	14.8	0.007735	45.5	0.01843	108	154	168
Children 1-6 years	0.003680	14.7	0.008604	50.6	0.013911	81.8	132	147
Children 7-12 years	0.002940	11.8	0.006208	36.5	0.008852	52.1	89	100
Females 13-50 years	0.001945	6.48	0.007637	76.4	0.004756	47.6	124	130

(a) Percent of aPAD = (Exposure ÷ aPAD) x 100%. aPAD for the general population = 0.25 and 0.17 mg/kg/day for benomyl and MBC, respectively, aPAD for females (13-50) = 0.03 and 0.01 mg/kg/day for benomyl and MBC, respectively and aPAD for children subgroups = 0.025 and 0.017 mg/kg/day for benomyl and MBC, respectively.

(b) Sum of %aPAD for MBC.

'(c) Percent of the MBC PAD = (Total exposure in MBC equivalents ÷ aPAD for MBC) * 100%. This is equivalent to the sum of %aPAD from benomyl + %aPAD from MBC. This is considered appropriate because the aPAD are based on the same effects for each population (i.e., testicular effects for all populations except females, where developmental effects were observed).

5.2 Short-Term Aggregate Risk

5.2.1 Aggregate 1: Benomyl and MBC (from Benomyl Uses)

Short-term aggregate risk estimates were not conducted for benomyl or MBC because no short-term non-occupational exposures are anticipated based on registered uses (i.e., benomyl is not registered for residential uses).

5.2.2 Aggregate 2: Benomyl and MBC from All Uses

5.2.2.1 Aggregate Short-Term Risk Assessment

For this assessment, HED evaluated the aggregate exposures to MBC resulting from registered uses of benomyl, thiophante methyl and MBC. As noted previously, MBC is a common metabolite of both fungicides. The short-term aggregate risk estimate includes chronic dietary (food and water) from benomyl and thiophante methyl uses, and short-term non-occupational exposures to MBC (from thiophanate-methyl and MBC uses). Because thiophante methyl has residential and non-occupational uses (i.e., lawns, golf courses and residential orchards), the potential exposure to MBC from these uses was estimated and added to the chronic dietary exposure. The residential uses for MBC (i.e., as a paint additive) were also added to the chronic dietary MBC exposure.

Table 11 presents the aggregate exposure estimates for MBC from diet and residential/non-occupational uses. Based on thiophanate-methyl uses, it was assumed that children (1-6 years) could be exposed to MBC residues through contacting treated residential turf, and through turf mouthing, and incidental ingestion of residues on turf (i.e., hand to mouth activities). Children 7-12 years could contact MBC residues and be dermally exposed during mowing activities, harvesting fruit from a residential orchard, and playing golf. However, for this assessment, only the highest exposure scenario, harvesting fruit was aggregated with dietary exposures, because the dermal exposures from mowing and golfing were approximately an order of magnitude lower than the fruit harvesting exposures. Female residents were assumed to have MBC dermal exposures through harvesting treated fruit and contact with treated residential turf. Potential dermal exposures from mowing and golf activities were approximately an order of magnitude lower, and therefore, would have a negligible contribution. The results of this exposure analysis are summarized in the attached memo summarizing MBC exposures from thiophanate-methyl uses (G. Bangs to D. Smegal, March 8, 2001, D273295), and are presented in detail in the Occupational /Residential Exposure Chapter for the Reregistration Eligibility Document for Thiophante-Methyl (D271922, March, 2000). Residents that apply thiophanate-methyl products to lawn and ornamentals are only expected to be exposed to thiophanate-methyl, and not MBC, because MBC is formed in the environment after application.

In addition, based on MBC registered uses, it was assumed that adult residents could be exposed to MBC during painting activities (i.e., dermal and inhalation exposure during painting) and through the diet (food and water). The dermal and inhalation exposures associated with airless sprayer were used in the aggregate assessment. Details of the residential exposure assessment for registered MBC uses are presented in the Attached memo from G. Bangs to D. Smegal, March, 2001. For this painting scenario, an adult resident was assumed to apply 2 gallons of paint containing 0.5% ai MBC, and wear short pants, short-sleeved shirt and no gloves. Exposure estimates were based on data from PHED. It was not considered reasonable to aggregate these MBC exposures with the lawn and orchard MBC exposures resulting from thiophanate-methyl

use. Post application exposures to paint vapors containing MBC is considered a long-term exposure and consequently is considered in the cancer aggregate assessments (below). Long-term inhalation exposures were not aggregated with non-cancer risks because the endpoint of concern (respiratory effects) is different than the chronic oral endpoint (liver effects).

All short-term oral exposures were compared to the short-term oral endpoint for MBC, in accordance with HED policy. As shown on Table 11, for children the dermal MOE risk estimates were not aggregated with oral exposures because the dermal endpoint is based on a different effect (i.e., decreased body weight and food consumption for oral and developmental effects for dermal). For females, both oral and dermal risk estimates were aggregated because both endpoints are based on the identical NOAEL of 10 mg/kg/day for developmental effects, and decreased body weight and food consumption. The dermal exposure estimates was adjusted for 3.5% dermal absorption in calculating the dermal risk estimates. It is not appropriate to aggregate the inhalation MOEs with the oral and dermal MOEs because the inhalation NOAEL is based on respiratory effects. As shown on table 11, for females two aggregate MOEs are presented (1) benomyl and thiophanate-methyl uses resulting in MBC exposure, and (2) benomyl and MBC uses resulting in MBC exposure. It was not considered reasonable to assume an individual could be exposed to all possible MBC sources simultaneously. The aggregate MOE for benomyl and MBC (from all uses) for developmental effects is 620, which exceeds HED's level of concern.

5.2.2.2 Short-Term DWLOC Calculations

Aggregate potential MBC exposures, along with the EFED estimated EECs are presented on Table 12. The highest long term EFED MBC EECs are 7.2 and 730 µg/L from benomyl and thiophanate-methyl use, respectively. However, because the EECs are based on tier I GENEEC modeling, it is HED policy to divide these EECs by a factor of 3 (HED SOP 99.5, M. Stasikowski, 8/1/99). Therefore, the long-term MBC EECs are 2.4 and is 243 µg/L, for benomyl and thiophante methyl use, respectively. As shown, the combined potential MBC exposure from food and residential use alone exceed HED's level of concern for children 1-6 years and females 13-50 years, and therefore any water exposure would only contribute to the exposures of concern. For these subpopulations, the short-term DWLOCs are effectively zero. For children 7-12 years, the long-term EEC in surface water is greater than the DWLOC, and therefore exceeds HED's level of concern. Therefore, **aggregate potential short-term exposure to MBC resulting from food, water and residential use due to benomyl and MBC uses exceeds HED's level of concern for children and females (13-50 years).** This analysis is considered reasonable because, HED assumed that there could be simultaneous dietary and residential exposures to MBC from benomyl and thiophanate-methyl or benomyl and MBC uses (but not from all three registered pesticides).

Table 11
Summary of Aggregate Short-Term Exposure
Chronic Diet and Short-Term Residential Use
Aggregate 2: Benomyl and MBC (From All Uses) (a)
(Excludes Water)

Population Subgroup	Benomyl (Target MOE $1000)		MBC +other metabolites (from benomyl)	MBC +other metabolites (from Thiophante Methyl) (Target MOE $1000)			MBC (from MBC Uses) (Target MOE $1000)		Total Aggregate MOE Estimate (c) (Target MOE $1000)		
	Chronic Diet Exposure Benomyl (mg/kg BW/day)	Chronic Diet Exposure as MBC equivalents (mg/kg BW/day)/ MOE	Chronic Diet Exposure (mg/kg BW/day)/ MOE (Target $ 1000)	Chronic Diet Exposure (mg/kg BW/day)/ MOE	Short-Term Residential Exposure (mg/kg/day)/ MOE		Short-Term Residential Exposure (mg/kg/day)/ MOE		Dermal	Inhalation	Oral and/or Dermal
					Oral	Dermal (b)	Dermal (b)	Inhalation (d)			
Children (1-6 years)	0.000072	0.000049 MOE = 200,000 (9BW and FC)	0.000167 MOE = 60,000 (9BW and FC)	0.000501 MOE = 20,000 (9BW and FC)	0.0116 (f) MOE = 860 (9BW and FC)	0.049 (0.0017 absorbed) MOE = 5,900 (develop-mental)	NA	NA	5,900 (develop-mental; MBC only)	NA	**810 (9BW and FC; oral only)**
Children (7-12 years)	0.000047	0.000032 MOE = 310,000 (9BW and FC)	0.000107 MOE = 93,000 (9BW and FC)	0.000294 MOE = 34,000 (9BW and FC)	none	0.026 (0.00091 absorbed) (e) MOE= 11,000 (develop-mental)	NA	NA	11,000 (develop-mental; MBC only)	NA	23,000 (9BW and FC; oral only)
Females (13-50 years)	0.000040	0.000013 MOE = 770,000 (9BW and FC/develop-mental)	0.00009 MOE = 110,000 (9BW and FC/ developmental)	0.00012 MOE= 83,000 (9BW and FC/develop-mental)	none	0.381 (0.0134 absorbed) (e) MOE =750 (develop-mental)	0.457 (0.016 absorbed) MOE = 620 (develop-mental)	0.0042 MOE = 230 (respira-tory)	NA	**230 (respiratory)**	**760 (benomyl and TM uses; 9BW and FC/ developmental)** **620 (benomyl and MBC uses; 9BW and FC/ developmental)**

BW=body weight; FC= food consumption

(a) MOE for MBC equivalents calculated based on short-term oral NOAEL of 10 mg/kg/day for decreased body weight and food consumption, short-term dermal NOAEL of 10 mg/kg/day for dermal (with 3.5% dermal absorption factor) and 0.96 mg/kg/day for inhalation. Benomyl converted to MBC equivalents based on the RPF approach, with RPFs of 0.33 and 0.68 for females and children, respectively.

(b) Exposure adjusted for 3.5% dermal absorption factor.

(c) Sum of MOEs for MBC. For children, dermal and oral MOEs were not combined because the NOAELs are based on different endpoints (i.e. dermal based on developmental effects and oral NOAEL based on decreased body weight and food consumption). For females (13-50 years), inhalation MOE was not aggregated with oral and dermal MOEs because the endpoint (respiratory effects) is different than the dermal and oral NOAEL based on developmental effects and decreased body weight and food consumption. MOE = 1 / (1/MOE diet + 1/MOE oral + 1/MOE dermal + 1/MOE inhalation).

(d) Inhalation NOAEL of 0.96 mg/kg/day, based on respiratory effects, was used to assess MBC inhalation exposure.
(e) For children 7-12 years, dermal exposure from harvesting fruit, which has highest dermal exposure. For females 13-50 yrs, dermal exposure from harvesting fruit and dermal lawn contact, in addition to broadcast application of liquid lawn treatment (handler exposure). Postapplication dermal exposure from mowing lawns and golfing were approximately an order of magnitude lower.
(f) Includes turf mouthing, and hand to mouth MBC exposure for lawns treated with thiophanate-methyl.

Table 12
Aggregate MBC DWLOCs for Short-Term Non-Cancer Exposures
Aggregate 2: MBC From All Uses

Population Subgroup	NOAEL or LOAEL (mg/kg/day)	Target MOE	Maximum Exposure (MBC Acute PAD) (mg/kg/day)	MBC Average Chronic Food Exposure (mg/kg/day) (a)	MBC Residential Exposure (mg/kg/day) (b)	Potential MBC Max. Water Exposure (mg/kg/day) (c)	Long-Term Surface Water EEC GENEEC (µg/L)	Long-term Ground Water EEC SCI-GROW (µg/L)	Short-Term DWLOC (µg/L) (d,e,f)
Children (1-6 years)	10	1000	0.01	0.000717	0.0116	None	2.4 (benomyl use)	0.14 (benomyl use)	Zero (no room)
Children (7-12 years)	10	1000	0.01	0.000433	None	0.0096	243 (TM use)	15 (TM use)	96
Females (13-50 years)	10	1000	0.01	0.000223	0.016 (g)	None			Zero (No room)

TM = thiophanate methyl
(a) Values from Table 11 represent the sum of MBC dietary exposure from benomyl and Thiophante methyl use. Includes benomyl exposure as MBC equivalents.
(b) Dermal exposure was excluded for estimate for children because dermal NOAEL is based on developmental effects, while the acute oral NOAEL is based on testicular effects. For females, absorbed dermal exposure from MBC paint application was used to calculate DWLOC since this exposure is higher than dermal exposure from thiophanate-methyl uses. Inhalation exposures were not included because of a different toxicity endpoint (respiratory effects).
(c) Potential maximum water exposure (mg/kg/day) = Acute PAD (mg/kg/day) - [Chronic Food Exposure + short-term Residential Exposure (mg/kg/day)]. Includes MBC residential exposure from Thiophante Methyl use for children or MBC as a paint additive for females.
(d) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/µg) x water consumed daily (L/day)].
(e) HED default body weights are: adult females, 60 kg; and children, 10 kg for children.
(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.
(g) Based on MBC exposures as a paint additive and excludes residential exposure from TM uses (which were lower than paint exposures).

5.3 Intermediate-Term Aggregate Risk

5.3.1 Aggregate 1: Benomyl and MBC (from Benomyl Uses)

Intermediate-term aggregate risk estimates were not conducted for benomyl or MBC because no intermediate-term non-occupational exposures are anticipated based on registered uses (i.e., benomyl is not registered for residential uses).

5.3.2 Aggregate 2: Benomyl and MBC from All Uses

5.3.2.1 Aggregate Intermediate-Term Risk Assessment

Some of the intermediate-term residential post application exposures for children playing on treated lawns result in MOEs less than 1,000 for MBC, and therefore already exceed HED's level of concern based on a screening-level assessment using the residential SOPs. Therefore, any additional intermediate-term-term exposures through food and drinking water would result in MOEs that would further exceed HED's level of concern. DWLOCs for intermediate-term exposures to MBC in drinking water were not calculated, because the DWLOCs are effectively zero. Consequently, an aggregate assessment for benomyl and MBC from all uses was not conducted**.**

5.4 Chronic Non-Cancer and Cancer Aggregate Risk

The chronic aggregate risk estimate to benomyl and MBC addresses exposure from food and water. For the Tier III chronic dietary exposure analysis, PDP monitoring data and field trial data, in conjunction with percent crop treated data were used to assess dietary exposures.

5.4.1 Aggregate 1: Benomyl and MBC (from Benomyl Use)

5.4.1.1 Aggregate Chronic Non-Cancer and Cancer Risk Assessment

Non-Cancer Aggregate

The benomyl chronic noncancer dietary risk estimates range are less than 1% of the cPAD for benomyl, with children 1-6 years being the highest exposed population subgroup (0.6% of the cPAD). For MBC, the chronic noncancer dietary risk estimates range from 0.4% to 6.7%, with highest risk estimates for children 1-6 years (6.7% of the cPAD). Thus, the chronic dietary (food) risk estimate associated with benomyl or MBC exposure individually is below the Agency's level of concern.

Because benomyl and MBC have common chronic toxicity (liver effects), and because individuals are likely to consume both chemical residues on benomyl-treated commodities, it is appropriate to add benomyl and MBC chronic dietary risk estimates. The aggregate chronic dietary risk estimates include exposure to benomyl and MBC residues in food and water; there are no uses that could result in residential exposure. Average chronic dietary food risk estimates are below the Agency's level of concern. The total dietary exposure to benomyl and MBC for the highest exposed population subgroup, children 1-6 years, is 7.2% of the cPAD for liver effects, leaving nearly 93% of the cPAD available for exposure through drinking water.

Cancer Aggregate

The cancer aggregate risk estimate also includes chronic dietary exposures from food and water because there are no residential uses or non-occupational exposures to benomyl or MBC (resulting from benomyl use). Total benomyl and MBC dietary cancer risk estimate is $3x10^{-7}$ for a 70 year exposure to the general U.S. population based on a refined Tier 3 dietary exposure analysis. This cancer risk estimate does not exceed HED's level of concern.

5.4.1.2 Chronic Non-Cancer and Cancer DWLOC Calculations

As noted previously, all benomyl dietary exposures were converted to MBC equivalents using the RPF approach. The DWLOCs were then estimated using the cPAD for MBC and by combining the average dietary exposure as MBC equivalents.

The chronic non-cancer and cancer DWLOC values are presented in Table 13. For each population subgroup listed, the chronic PAD and the chronic dietary (food) exposure (from Table 7) for that subgroup were used to calculate the chronic DWLOC for the subgroup, using the formulas in footnotes of Table 13.

Using conservative screening-level models, the estimated concentration of MBC in groundwater (SCI-GROW) is 0.14 µg/L. The long-term EEC for MBC in surface water (GENEEC) is 2.4 µg/L (i.e., 7.2 µg/L divided by 3 based on HED policy for long-term GENEEC results). Because benomyl rapidly (within hours) degrades to MBC in water, EFED did not provide a surface water EEC for benomyl.

As shown, both the non-cancer and cancer DWLOCs are below the EECs for MBC. As noted previously, when EECs are **less** than DWLOCs, HED considers the aggregate risk [from food + water] to not exceed HED's level of concern. Therefore, HED concludes with reasonable certainty that **chronic noncancer and cancer aggregate exposure to benomyl and MBC (from benomyl use) does not exceed the HED's level of concern.**

However, it should be noted that the EECs do not reflect dilution from source to tap nor do they reflect water treatment. HED also notes that the concentration estimate for long-term concentrations of MBC in surface water from GENEEC represents a 56-day average number only, and not an annual average concentration (which is appropriate for use in chronic assessments), nor a multi-year mean (which is appropriate for use in cancer assessments). Although HED divides this 56-day average concentration by a factor of 3, the resulting concentration value may not represent a long-term concentration value and should be refined for chronic/cancer assessments.

Table 13 DWLOCs for Chronic Non-Cancer and Cancer Aggregate Dietary Exposure Aggregate 1: Benomyl and MBC (from Benomyl Use)							
Population Subgroup (a)	**MBC Chronic PAD (mg/kg/day)**	**Q1* $(mg/kg/day)^{-1}$**	**Total Average Chronic Food Exposure as MBC Equivalents (mg/kg/day) (b)**	**Potential MBC Max. Water Exposure (mg/kg/day) c)**	**MBC Surface Water EEC GENEEC (µg/L)**	**MBC Ground Water EEC SCI-GROW (µg/L)**	**Chronic DWLOC (µg/L) (d,e,f)**
Non-Cancer							
U.S. Population	0.025	$2.39x10^{-3}$	0.000099	0.0249	2.4	0.14	872
All Infants (< 1 Year)	0.0025		0.0001046	0.00239			24
Children (1-6 years)	0.0025		0.00018	0.0023			23
Females (13-50 years)	0.0025		0.000098	0.0024			72
Cancer							
U.S. Population	0.0025	$2.39x10^{-3}$	0.000124	0.00029	2.4	0.14	10.3

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.

(b) Values are from Table 7, and represent the sum of benomyl and MBC dietary exposure. Benomyl values were converted to MBC equivalents using the RPF approach.

C) Maximum Water Exposure (mg/kg/day) (non-cancer) = Chronic PAD (mg/kg/day) - [Chronic Food Exposure (mg/kg/day). Maximum Water Exposure (mg/kg/day) (cancer) = 1x10-6/Q1* - chronic food exposure (mg/kg/day). Benomyl and MBC have no registered residential uses.

(d) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/µg) x water consumed daily (L/day)].

(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.

(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

5.4.2 Aggregate 2: Benomyl and MBC From All Uses

5.4.2.1 Aggregate Chronic Non-Cancer and Cancer Risk Assessment

Chronic aggregate exposure includes all MBC chronic dietary exposure resulting from registered uses of both benomyl and thiophante methyl. As noted previously, MBC is a common metabolite of both fungicides. In addition, benomyl and MBC have similar toxic effects (i.e., liver effects and liver tumors) and therefore were added together. Chronic residential exposures to MBC are not anticipated based on registered uses for thiophante methyl. While there are potentially chronic inhalation exposures to MBC vapors from use of MBC as a paint additive, these exposures were not considered in the non-cancer aggregate assessment because the endpoint of concern (respiratory effects) is different from the chronic oral endpoint of concern (liver effects). However, these potential chronic inhalation exposures are assessed in the cancer aggregate

assessment below.

This assessment is conservative, because benomyl and thiophanate-methyl are used on the same crops, and it is likely that a grower would use benomyl or thiophanate-methyl (and not both together) because both fungicides control similar pests. Consequently, it is more likely that individuals will be exposed to MBC and 2-AB from benomyl or thiophanate-methyl. For example, both fungicides are registered on some of the same crops including: almonds, apples, green and dry beans, bananas, squash, cucumbers, melons, peaches, plums, peanuts, soybeans, strawberries and wheat. In addition, although there are no PDP data for thiophanate-methyl, it is possible that the PDP data for benomyl include MBC and 2-AB environmental residues from thiophanate-methyl application. PDP data are available for five commodities (apples, bananas, green beans, peaches, and strawberries) that have both benomyl and thiophanate-methyl tolerances. The PDP data results, however are only for benomyl (and not for MBC). Because the PDP analytical method quantifies total benomyl, MBC and 2-AB residues from all sources (both benomyl and thiophanate-methyl), it is possible that the aggregate dietary MBC exposure and risk estimates (from benomyl and thiophanate-methyl use) may be overestimated to an unknown degree. BEAD estimates that the annual usage of benomyl is approximately two times greater than thiophanate-methyl.

Non-Cancer Aggregate

As shown on Table 14 the aggregate chronic food only non-cancer risk estimates for MBC and benomyl, combined are below 100% of the PADs, and therefore do not exceed HED's level of concern. The highest exposed group is children 1-6 years of age, with an aggregate exposure equivalent to 28% of the PAD for both dietary exposure to MBC and benomyl.

Cancer Aggregate

For this assessment, HED evaluated the aggregate exposures to MBC resulting from registered uses of benomyl, thiophante methyl and MBC. Chronic aggregate cancer exposure, includes all MBC chronic dietary exposure resulting from both benomyl and MBC. In addition, benomyl and MBC have the same toxic effects (i.e., liver effects) and Q_1* based on mouse liver tumors, and therefore were added together. Chronic residential exposures to MBC are not anticipated based on registered uses for thiophante methyl. There are potential chronic inhalation exposures to MBC from MBC's registered use as a paint additive (i.e., dermal and inhalation exposures to a resident painter, and chronic inhalation to vapors in a painted room). Therefore, these MBC inhalation exposures were included in the aggregate risk estimates.

As shown on Table 15 the aggregate cancer dietary risk estimates (food only) for MBC and benomyl, combined is $9x10^{-7}$.

5.4.2.2 Chronic Non-Cancer and Cancer DWLOC Calculations

As noted previously, all benomyl dietary exposures were converted to MBC equivalents using the RPF approach. The DWLOCs were then estimated using the cPAD for MBC and by combining the average dietary exposure as MBC equivalents.

The chronic non-cancer and cancer DWLOC values are presented in Table 16. For each population subgroup listed, the chronic PAD and the chronic dietary (food) exposure (from Table 7) for that subgroup were used to calculate the chronic DWLOC for the subgroup, using the

formulas in footnotes of Table 16.

The highest long term EFED MBC EECs are 2.4 and 243 µg/L from benomyl and thiophante methyl use, respectively. As shown on Table 16, the EFED surface water EEC of 243 µg/L from thiophante methyl use is greater than the DWLOCs for children and females 13-50 years of 18-21 µg/L and 68 µg/L, respectively, which exceeds HED's level of concern for chronic, non-cancer effects. The DWLOC for the U.S. Population is above the EECs, indicating that aggregate exposure to this population does not exceed HED's level of concern for chronic non-cancer effects.

As shown on Table 15 the aggregate cancer dietary risk estimates (food only) for MBC and benomyl, combined is $9x10^{-7}$. As shown on Table 16, the cancer DWLOC is 1.4 µg/L, which is less than the long-term EECs of 2.4, 15 and 243 µg/L, and therefore, exceed HED's level of concern.

Therefore, **HED concludes the aggregate exposure to benomyl and MBC from all uses on food and residential potential residues in water exceeds HED's level of concern for chronic non-cancer and carcinogenic effects.** The cancer risk estimates for MBC use as a paint additive are conservative, because they are based on high end assumptions for occupancy, air exchange rates used in the air model, and assume no degradation or matrix effects of the paint. It should be noted that benomyl exposures had a minimal impact the non-cancer aggregate risk estimates. This is because chronic dietary benomyl exposures represent less than 1% of the benomyl cPAD for liver effects.

As noted previously, the EECs do not reflect dilution from source to tap nor do they reflect water treatment. HED also notes that the concentration estimate for long-term concentrations of MBC in surface water from GENEEC represents a 56-day average number only, and not an annual average concentration (which is appropriate for use in chronic assessments), nor a multi-year mean (which is appropriate for use in cancer assessments). Although HED divides this 56-day average concentration by a factor of 3, the resulting concentration value may not represent a long-term concentration value and should be refined for chronic/cancer assessments.

Table 14
Aggregate 2: Summary of Aggregate Chronic Non-Cancer Diet Exposure and Risk Estimates
Benomyl and MBC Tier 3 Chronic Dietary
Exposure Analysis by DEEM
(Excludes Water)

Population Subgroup	Benomyl		MBC +other metabolites (from benomyl)		MBC +other metabolites (from Thiophante Methyl)		Total Benomyl and MBC Exposure	Total Risk Estimate for MBC Food Only	Total Risk Estimate for Benomyl and MBC Food Only
	Exposure (mg/kg BW/day)	%cPAD (a)	Exposure (mg/kg BW/day)	%cPAD (a)	Exposure (mg/kg BW/day)	%cPAD (a)	Exposure as MBC Equivalents (mg/kg/day) (d)	%cPAD (b)	%cPAD by target organ (c)
US Population	0.000042	0.03	0.000091	0.4	0.000163	0.7	0.000280	1.1	1.1
All infants (< 1 yr)	0.000045	0.3	0.000096	3.8	0.000343	13.7	0.000448	18	18
Children (1-6 years)	0.000072	0.6	0.000167	6.7	0.000501	20	0.000683	27	28
Children (7-12 years)	0.000047	0.4	0.000107	4.3	0.000294	11.8	0.000410	16	16
Females 13-50 years	0.000040	0.3	0.00009	3.6	0.00012	4.8	0.000218	8	8

(a) Percent of cPAD = (Exposure ÷ cPAD) x 100%. cPAD for the general population = 0.13 and 0.025 mg/kg/day for benomyl and MBC, respectively, cPAD for females (13-50 years) = 0.013 and 0.0025 mg/kg/day for benomyl and MBC, respectively and cPAD for children subgroups = 0.013 and 0.0025 mg/kg/day for benomyl and MBC, respectively.

(b) Sum of %cPAD for MBC.

‘(c) Percent of MBC cPAD = (total exposure in MBC equivalents ÷ cPAD for MBC)*100%. This is also equivalent to the sum of the %cPAD for benomyl and MBC+2-AB. This is considered appropriate because the cPADs are based on the same adverse effect for benomyl and MBC.

(d) Benomyl exposure adjusted using RPFs of 0.192 for all populations to account for the differences in cPADs for benomyl and MBC.

Table 15
Aggregate 2: Summary of Aggregate Cancer Risk Estimates
Benomyl and MBC Tier 3 Chronic Dietary
Exposure Analysis by DEEM
(Excludes Water)

Population Subgroup (a)	Benomyl as MBC equivalents		MBC +other metabolites (from benomyl)		MBC +other metabolites (from Thiophante Methyl)		MBC (from MBC Use as Paint Additive)		Total Benomyl and MBC
	Exposure (mg/kg BW/day) (d)	Lifetime Cancer Risk Estimate (a)	Exposure (mg/kg BW/day)	Lifetime Cancer Risk Estimate (a)	Exposure (mg/kg BW/day)	Lifetime Cancer Risk Estimate (a)	Exposure (mg/kg BW/day) (c)	Lifetime Cancer Risk Estimate (a)	Lifetime Cancer Risk Estimate (b)
US Population	0.000028	6.7×10^{-8}	0.000096	2.3×10^{-7}	0.000163	3.9×10^{-7}	9×10^{-5}	2.2×10^{-7}	9×10^{-7}

(a) Lifetime cancer risk = Dietary Exposure x Q1*, where Q1* is 2.39×10^{-3} $(mg/kg/day)^{-1}$

(b) Total cancer risk is the sum of cancer risks from benomyl and MBC.

(c) Sum of exposure to both residential handler during paint activities and to vapors following painting.

(d) Dietary benomyl exposure adjusted downwards by a factor of 0.66 to account for differences in molecular weight between MBC and benomyl because the Q1* is based on MBC tumor data.

Table 16: Aggregate 2: Aggregate MBC DWLOCs for Chronic Exposures Benomyl and MBC (all uses)									
Population Subgroup	**MBC Chronic PAD (mg/kg/ day)**	**Q1* $(mg/kg/day)^{-1}$**	**MBC Chronic Average Food Exposure (mg/kg/day) (a)**	**Total Food as MBC Equivalents (mg/kg/day) (f)**	**MBC (from MBC as Paint Additive) (mg/kg/day)**	**Potential MBC Max. Water Exposure (mg/kg/day) (b)**	**Long-Term Surface Water EEC GENEEC (µg/L)**	**Long-term Ground Water EEC SCI-GROW (µg/L)**	**Chronic DWLOC (µg/L) (c,d,e)**
Non-Cancer									
US Population	0.025	$2.39x10^{-3}$	0.000272	0.000280	NA	0.0247	2.4 (benomyl use) 243 (TM use)	0.14 (benomyl use) 15 (TM use)	865
All infants (< 1 yr)	0.0025		0.000439	0.000448	NA	0.0020			20
Children (1-6 years)	0.0025		0.00067	0.000683	NA	0.0018			18
Children (7-12 years)	0.0025		0.00040	0.000410	NA	0.0021			21
Females 13-50 years	0.0025		0.00021	0.000218	NA	0.00228			68
Cancer									
US Population	0.0025	$2.39x10^{-3}$	0.000259	0.000287 (i)	0.00009 (h)	0.0000414	2.4 (benomyl use) 243 (TM use)	0.14 (benomyl use) 15 (TM use)	1.4

NA = not applicable.

(a) Exposure from Table 14 for non cancer and Table 15 for cancer exposure estimates. Sum of MBC from benomyl and TM use.

(b) Non-cancer Maximum Water Exposure (mg/kg/day) = cPAD (mg/kg/day) - [Chronic Food Exposure]. Cancer Maximum Water Exposure (mg/kg/day) = $(1x10^{-6} / Q_1^*)$ - [Chronic Food Exposure+ chronic residential exposures]. Benomyl has no chronic registered residential uses. MBC Cancer water exposure estimate also incorporates benomyl because MBC and benomyl have the same Q1*, and are present on the same food commodities.

(c) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [$(10^{-3}$ mg/µg) x water consumed daily (L/day)].

(d) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.

(e) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

(f) Sum of MBC equivalent exposure from Table 7 (benomyl + MBC) and MBC exposure from thiophante methyl on Table 14.

(g) MBC inhalation exposure not considered to non-cancer because the toxicity endpoint (respiratory effects) differs from the oral endpoint.

(h) Sum of exposure to both residential handler during paint activities and to vapors following painting.

(i) Cancer dietary exposure from Table 15.

6.0 CUMULATIVE EXPOSURE AND RISKS

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

EPA does not have, at this, time, available data to determine whether benomyl has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For purposes of this reregistration decision, EPA has assumed that benomyl does not have a common mechanism of toxicity with other substances.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether benomyl shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for benomyl need to be modified or revoked.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf
In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized by the summer of 2001.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

HED did not perform a cumulative risk assessment as part of this reregistration review for benomyl because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of benomyl. If HED identifies other substances that share a common mechanism of toxicity with benomyl, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

It is possible that benomyl and MBC may express toxicity and carcinogenicity through a common mechanism as the other benzimidazole compounds and, consequently these pesticides may be considered as a group when performing cumulative risk assessments in the future. It is

also noted that both benomyl and MBC are structurally related to several other benzimidazole compounds (primarily veterinary drugs) that are suspect carcinogens including albendazole, fenbendazole, mebendazole, oxfendazole and thiabendazole. Most of the benzimidazole compounds are regulated by the Center for Veterinary Medicine, Food and Drug Administration (FDA) as animal drugs. The potential carcinogenic effects of these compounds were reviewed by the Center for Veterinary Medicine, Food and Drug Administration (FDA). Thiabendazole also has agricultural uses.

7.0 OCCUPATIONAL EXPOSURE

Benomyl, Methyl 1-(Butyl-carbamoyl)-2-benzimidazolecarbamate, is a systemic fungicide that is widely used in agricultural settings. All residential uses and landscape uses have been canceled and are no longer supported by the registrant, DuPont. Therefore, no residential or non-occupational exposures are anticipated. There is potential for spray drift during aerial application, and at this time HED is developing guidance for characterizing exposures from this scenario. Benomyl is applied by most ground and aerial methods, and also applied as a seed treatment in dry or slurry form; a seedling treatment (conifers); and a dip treatment for seeds. Uses for which benomyl has been canceled include flowers; ornamentals; bulbs; shade trees; greenhouse (hydroponic/chemigation uses); dip treatment for sugarcane; drench treatment for strawberry plants; and post-harvest use on apples, citrus, pineapple, bananas, pears, and stone fruit.

Benomyl is formulated as a wettable powder (WP) and wettable powder in water soluble film (i.e., packets, WSP), both of which contain 50 percent active ingredient. An oil dispersible (OD) powder formulation is also registered, which is miscible with water, and available in water soluble pouch (WSP). The OD and OD/WSP have the same registration number (352-385) but are not yet sold or distributed in the U.S.

7.1 Handler

Occupational exposures to benomyl can occur during handling (mixing, loading and application activities). Because environmental fate data suggest that benomyl rapidly converts to MBC, all postapplication residues were assumed to be MBC. Details of the occupational exposure assessment are presented in the attached memorandum from G. Bangs to D. Smegal D, January 31, 2001, D269486.

Handler Exposure Scenarios

Based on the registered use patterns, HED has identified 11 major exposure scenarios for which there is potential occupational handler exposure during mixing, loading, and applying products containing benomyl to agricultural crops. These scenarios are as follows:

(1) mixing/loading wettable powders for airblast, groundboom, aerial, and chemigation application;
(2) applying sprays with an airblast sprayer to orchards, conifers and field crops;
(3) applying sprays with a groundboom sprayer to field crops;
(4) applying sprays with a fixed-wing aircraft to orchards, conifers and field crops;
(5) applying sprays with a helicopter;
(6a) mixing/loading/applying using a hose-end sprayer;
(6b) mixing/loading/applying using a tank with a hose-end sprinkler (mushrooms);

(7) mixing/loading/applying as a dry seed treatment in a planter box;
(8) mixing/loading/applying as a commercial seed treatment in slurry form;
(9) mixing/loading/applying as a commercial seedling treatment in dry or slurry form;
(10) mixing/loading/applying solution as a seed/seedling dip treatment and
(11) flagging aerial spray applications.

These occupational scenarios reflect a broad range of application equipment, application methods and use sites. There are currently insufficient data to evaluate scenarios 5, 8, 9, and 10, and additional data are requested for these registered uses.

Cancer risks were assessed for both private and commercial handlers. Private handlers are workers employed by typical agricultural establishments, while commercial handlers are workers employed by commercial operators or by very large agricultural establishments and apply benomyl approximately 10 times more days than a private handler.

For agricultural uses, application techniques include airblast, aerial, tractor-drawn equipment (groundboom or broadcast spreader), chemigation, open and closed mixing/loading systems, and hand held equipment.

For the agricultural handlers, the estimated exposures considered baseline protection (long pants and a long-sleeved shirt, no gloves, and an open cab or tractor), additional personal protective equipment (PPE, which includes a coveralls over a single layer of clothing and gloves and/or a dust/mist respirator), and engineering controls (water-soluble packets for wettable powders, closed mixing/loading systems for liquids and granulars and enclosed cabs/cockpits).

Data Sources and Assumptions

Except for one study provided by the Mushroom Institute, no chemical-specific data on handler exposure were submitted to the Agency for benomyl. Therefore, potential exposures resulting from handling and applying benomyl were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases.

Potential exposures were calculated using unit exposures from PHED multiplied by the amount of benomyl handled per day (i.e., lb ai/day). The amount of benomyl assumed handled per day was derived from the various application rates and the number of acres (or gallons of spray solution) that could be applied in a single day.

The duration of exposure is expected to be short-, and intermediate-term for occupational handlers. The exposure duration for short-term assessments is 1 to 7 days, while intermediate-term durations are 1 week to 6 months.

The crops on which benomyl is used, application rates, and the corresponding number of treatments per season are summarized below for the different benomyl formulations. Benomyl is

applied to conifers, grapes, trees nuts, mangoes, pome fruits, stone fruits, avocados, berries, citrus, and papayas at application rates of 0.5 to 1.5 pounds active ingredient (a.i.) per acre (lb ai/acre). This formulation can be applied from two to five times a season, with a seasonal maximum of 2.5 to 3 lb ai/acre for these crops. The wettable powder formulation is also applied to peanuts, rice, soybeans, beans, brassica, carrots, celery, cucurbits, garlic, tomatoes, wheat, sugar beets, and yams at application rates of 0.125 to 1 lb ai/acre. For these crops, benomyl in this formulation can be applied from three to twelve times a season, with a seasonal maximum of 1.5 to 3 lb ai/acre.

Benomyl is also applied as a seed treatment (beans, wheat, barley, oats, rye, brassica, chickpeas, and spinach) in dry or slurry form at a rate of 3 to 8 ounces ai/100 lb or seed; a seedling treatment (conifers) at a rate of 1 to 2.5 ounces ai/50 ounces clay; and a dip treatment (avocado seeds, wood grafts, garlic, sweet potatoes, yams, pineapples, and asparagus crowns) at a rate of 5 to 16 ounces ai/100 gallons of water.

Benomyl is applied to mushrooms at a rate of 0.0625 lb ai/1,000 square feet (sq ft) with hose-end type sprayers. It is applied a maximum of two times during the growing period, for a total of 0.125 lb ai/1,000 sq. ft. per growing period or "crop". (Note that there are several growing periods per year for each mushroom production bed).

Risk Characterization

A summary of the short- and intermediate-term risk estimates for baseline, PPE and engineering controls is presented in Table 17 for agricultural and commercial uses. Table 16 also provides a summary of the range of application rates assessed for benomyl.

Non-cancer risk estimates are expressed in terms of the Margin of Exposure (MOE). MOEs for occupational handlers were derived by dividing appropriate NOAEL for benomyl, shown on Table 3, by the daily dermal or inhalation exposure estimate. As noted previously, the short and intermediate-term dermal NOAEL of 500 mg/kg/day is from a dermal toxicity study in rabbits, and therefore, no dermal absorption adjustment is necessary. Inhalation exposure estimates were compared directly to the short- and intermediate-term inhalation NOAEL of 0.96 mg/kg/day from a 90 day rat inhalation toxicity study. Dermal and inhalation risk estimates were presented separately and not combined because of the different target organs.

Benomyl is also classified as a possible human carcinogen (class C) based on the presence of liver tumors in mice following dietary exposure. The oral Q_1^* for benomyl and MBC is 2.39×10^{-3} $(mg/kg/day)^{-1}$ based on MBC tumor data. The benomyl exposure was adjusted downward by a factor of 0.66 to reflect the ratio of MBC to benomyl molecular weights (based on Ad Hoc CARC memo, D. Smegal to D. Fuller, September 21, 2000, D269149). This cancer estimate was used to assess dermal and inhalation exposure to handlers. Because the cancer estimate is based on an oral study, a dermal absorption factor of 3.5% was applied, based on a study of benomyl dermal absorption in rats. It was conservatively assumed that inhalation absorption is equivalent to oral absorption (i.e., 100%).

For occupationally exposed workers, MOEs $\geq$100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) do not exceed HED's level of concern. MOEs below this level would represent a potential risk concern. A total dermal and inhalation MOE was not calculated because the toxicity endpoint differs between dermal (testicular effects) and inhalation (respiratory effects) exposures. Cancer risks are presented as a probability of developing cancer.

In general, the Agency is concerned whenever occupational cancer risk estimates exceed $1x10^{-4}$ (one in ten thousand) and will attempt to mitigate cancer risk to workers to a lower level, preferably to 10^{-6} or less, by the addition of various exposure risk mitigation measures.

Occupational risk estimates for handlers exposed to benomyl do not exceed HED's level of concern with label-required PPE or engineering controls. The results of the short- and intermediate-term agricultural handler assessments indicate that most of the potential exposure scenarios provide dermal and inhalation MOEs greater than or equal to 100 at baseline attire (i.e., long pants, long sleeved shirts, no gloves), while all of the 8 major scenarios quantitatively evaluated using label-required personal protective equipment (PPE) (long sleeved shirt, long pants, shoes, socks, and chemical-resistant gloves) or by using engineering controls (e.g., water soluble bags) have MOEs greater than or equal to 100. Benomyl handler total cancer risk estimates (dermal and inhalation combined) are in the range of $3.7x10^{-9}$ to $3.1x10^{-5}$ for baseline attire for private handlers and $1.1x10^{-8}$ to $1.3x10^{-4}$ for commercial handlers. All cancer risks were below $1x10^{-6}$ with label-required PPE and/or engineering controls, except scenario (7) mixing, loading and applying benomyl as an on-farm seed treatment in a planter box, where the commercial cancer risk is $5.6x10^{-6}$. In general, HED is concerned whenever occupational cancer risk estimates are within or exceed $1x10^{-6}$ to $1x10^{-4}$.

As noted previously, there are insufficient information and data to assess the slurry seed and seedling treatment uses, and dip applications (scenarios 8, 9 and 10) and additional data are requested to support these uses. Limited handler data are available for commercial seed treatment using liquid formulation. However, because it is likely that mixing, loading and applying a slurry will result in greater exposure than handling liquid formulation alone, the risk assessment for this scenario was not performed. HED requests data for these registered uses.

The agricultural handler assessments are believed to be reasonable representations of benomyl uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

C not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies

These uncertainties are inherent in most pesticide exposure assessments. The handler assessment were based upon conservative assumptions (e.g., maximum application rates, high daily acreage, 35-year exposure period) and therefore are believed to be protective of the handlers.

7.2 Postapplication

EPA has determined that there is potential exposure to persons entering treated sites (e.g., scouts and harvesters and other field workers) after application is complete. Occupational postapplication exposure to MBC can occur for agricultural workers during scouting, irrigation, cultivation, harvesting and handling seeds and seedlings. Details of the occupational exposure assessment are presented in the attached memorandum from G. Bangs to D. Smegal D, January 31, 2001, D269486.

Exposure Data and Assumptions

The duration of exposure is expected to be short- (1-7 days), intermediate- (1 week to 6 months) and long-term (greater than 6 months) for occupational postapplication during agricultural and

harvesting activities. Only mushroom workers are expected to have long-term postapplication exposure. Benomyl rapidly breaks down (hydrolyzes) to MBC within 24 hours after application based on EFED data. Therefore, it was conservatively assumed that postapplication exposures would be exclusively to MBC (which has lower NOAELs than benomyl) due to the complexity of determining relative decay rates of benomyl and MBC.

Based on toxicological criteria and potential for exposure, HED has conducted a dermal exposure assessment for occupational postapplication exposure to MBC. Inhalation is not expected be a significant postapplication exposure route.

Post-application exposure dislodgeable foliar residue (DFR) data were submitted for apples, grapes, and strawberries, and postapplication exposure data were submitted for mushrooms. All four studies are included in this assessment. Chemical-specific studies are not available for all activities and crops that are potentially treated with benomyl. Therefore, the assessment of postapplication exposures in this document is based on a grouping of activities associated with various representative crops. The potential for dermal contact during postapplication activities (e.g., harvesting) is assessed using a matrix of potential dermal contact rates by activity and associated crops with groupings of harvesting tree nuts and fruits, grape harvesting, mushroom harvesting and harvesting/scouting low- growing fruits and vegetables.

The revised HED Exposure Science Advisory Council Policy (Policy 003.1 revised August 7, 2000) was used to estimate worker postapplication exposures. Transfer coefficients are based primarily on data submitted to the Agency by the Agricultural Re-entry Task Force (ARTF). Data from the ARTF submitted studies are proprietary and compensation issues with ARTF may need to be addressed.

Postapplication Risk Characterization

As noted previously, it was conservatively assumed that postapplication exposures would be exclusively to MBC (which has lower NOAELs than benomyl). Therefore, MOEs for occupational handlers were derived by dividing the appropriate NOAEL for MBC, shown on Table 4, by the daily dermal exposure estimate. As noted previously, the short and intermediate-term dermal NOAEL of 10 mg/kg/day is from an oral rat developmental study that observed decreased fetal body weight and other fetal and maternal changes. Because a developmental study was selected, a body weight of 60 kg for the median female body weight was to calculate worker exposures. An oral NOAEL of 2.5 mg/kg was selected for long-term dermal exposure to MBC, based on liver changes in a 2-year dog study. Because the dermal endpoints are based on oral studies, a dermal absorption factor of 3.5% was applied, based on a study of benomyl dermal absorption in rats.

MBC is also classified as a possible human carcinogen (class C) based on the presence of liver tumors in mice following dietary exposure. The oral Q_1^* for MBC is 2.39×10^{-3} $(mg/kg/day)^{-1}$. This cancer estimate was used to assess dermal exposure to postapplication workers. Because the cancer estimate is based on an oral study, a dermal absorption factor of 3.5% was applied, based on a study of benomyl dermal absorption in rats.

As noted previously, MOEs $100 do not exceed HED's level of concern for occupationally exposed workers. MOEs below this level would represent a potential risk concern. A total dermal and inhalation MOE was not calculated for MBC because the toxicity endpoint differs between dermal (developmental effects) and inhalation (respiratory effects) exposures.

Table 18 summarizes the MBC postapplication risk estimates. The results of the short-, and intermediate-term dermal postapplication assessments for workers exposed to MBC at agricultural use sites indicate that the current Worker Protection Standard (WPS)-required restricted entry interval (REIs) of 24 hours is adequate. The potential for dermal contact during postapplication activities (e.g., harvesting) is assessed using a matrix of potential dermal contact rates by activity. Chemical-specific postapplication exposure Dislodgable Foliar Residue (DFR) data were submitted for apples, grapes, strawberries and mushrooms. These data were used along with HED standard transfer coefficients to assess potential exposures to workers reentering treated sites. The estimates showed that short- and intermediate-term dermal post-application worker exposures to MBC resulted in MOEs of greater than 100 on the first day after application of benomyl for all crops and activities, and therefore do not exceed HED's level of concern. Long-term (greater than 180 days/year) MOEs for harvesting mushrooms, strawberries, blueberries, tomatoes, and pineapples are also greater than 100.

Cancer risk estimates for all postapplication scenarios were less than $1x10^{-5}$ at 7 days after treatment (range $<5.3x10^{-8}$ to $9x10^{-6}$) at seven days after treatment. Given that benomyl may be reapplied at varying intervals, and that cancer risks are estimated based on typical exposures, the seventh-day postapplication DFR data were used to calculate re-entry worker cancer risk estimates (i.e., it is unlikely that workers would consistently be exposed to DAT 1 residue levels). Cancer risks from citrus harvesting ($9x10^{-6}$) do not reach a $1x10^{-6}$ cancer risk until residues from the 16th day after treatment with benomyl are used in the calculations. This means that workers would have to enter citrus groves for harvesting, on average, on the 16th day after treatment to ensure that risks are at or below 10^{-6}. However, benomyl is not typically applied to citrus trees close to harvest. Because other activities (i.e., thinning, pruning, weeding) have transfer coefficients that are more than half the transfer coefficient for harvesting, cancer risks would be expected to be equal to or less than 10^{-6} for these activities on DAT 7. The Agency also assumes workers performing postapplication work will only wear a single layer garment and no gloves while in the field. Wearing additional clothing while performing field work, although decreasing skin exposure, may result in heat stress and endanger the workers' health. The use of fabric gloves when handling pesticide-contaminated articles may actually increase worker exposure by accumulating and holding the chemicals next to the skin.

The occupational postapplication assessments are believed to be reasonable representations of benomyl uses. The long-term post application scenarios are considered conservative high-end estimates and are sufficient for a screening-level exposure and risk assessment. While some individuals may exceed these estimates, the Agency believes that most workers in each group would have fewer than 180 days of exposure than are estimated for the indicator crops. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- extrapolating exposure and DFR data by the amount of active ingredient handled or applied;
- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies; and
- application timing in comparison to actual potential postapplication exposure scenarios.

These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the worker. For example, conservative assumptions (e.g., maximum application rates, high daily acreages, 35-year exposure period, and first day-after-treatment residues) were used to estimate exposures and risks to

workers.

Table 17
Benomyl: Summary of Occupational Handler Short & Intermediate-term Exposure & Cancer Risk Estimates

Exposure Scenario (Scenario #)	Application Rate (lb ai) (crops) (a)	Daily Acreage or Other Unit (b)	Baseline (c)			PPE: Single-layer Clothing + Gloves, Dust/Mist Respirator			Engineering Controls (d)		
			Dermal MOE	Inhalation MOE	Cancer Risk Private/ Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial
(1a) Mixing/Loading Wettable Powder for Airblast Application	0.5 (conifers, berries)	40	470	**78**	5.3E-07/ **5.2E-06**	10,000	390	4.4E-08/ 4.5E-07	Not necessary		
	0.75 (pome fruits, grapes)		320	**52**	6.4E-07/ **6.3E-06**	6,900	260	5.3E-08/ 5.3E-07			
	0.875 (tree nuts)		270	**45**	5.4E-07/ **5.5E-06**	5,900	220	4.6E-08/ 4.7E-07			
	1 (mangoes, stone fruit, avocados, papayas)		240	**39**	6.4E-07/ **6.3E-06**	5,100	200	5.3E-08/ 5.3E-07			
	1.5 (citrus)		160	**26**	6.4E-07/ **6.3E-06**	3,400	130	5.3E-08/ 5.1E-07			
(1b) Mixing/Loading Wettable Powder for Groundboom Application	0.125 (peanuts)	80	950	160	5.3E-07/ **1.6E-06**	Not necessary		4.4E-08/ 1.3E-07	Not necessary		
	0.25 (sugar beets, cucurbits, celery, chinese cabbage, mustard greens)		470	**78**	6.4E-07/ **6.3E-06** (highest crops)	10,000	390	5.3E-08/ 5.4E-07 (highest crops)			
	0.5 (carrots, tomatoes, corn)		240	**39**	6.4E-07 / **6.3E-06 (carrots,crn) 1.1E-06/ 1E-05 (tomatoes)**	5,100	200	8.8E-08 / 8.8E-07 (highest crop)			
	1 (beans, brassica, yams)		120	**20**	**1.7E-06 / 1.7E-05**	2,600	**98**	1.4E-07/ **1.4E-06**	45,000	3,500	5.7E-09 / 5.7E-08

Table 17
Benomyl: Summary of Occupational Handler Short & Intermediate-term Exposure & Cancer Risk Estimates

Exposure Scenario (Scenario #)	Application Rate (lb ai) (crops) (a)	Daily Acreage or Other Unit (b)	Baseline (c)			PPE: Single-layer Clothing + Gloves, Dust/Mist Respirator			Engineering Controls (d)		
			Dermal MOE	Inhalation MOE	Cancer Risk Private/ Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial
	0.5 (soybeans)	200	**95**	**16**	**5.3E-06/ 1.6E-05**	2,100	**78**	1.8E-07/ 5.3E-07	36,000	2,800	not necessary
	1 (wheat, rice)		**47**	**7.8**	**4.2E-06/ 4.2E-05**	1,000	**39**	3.5E-07/ **3.6E-06**	18,000	1,400	1.4E-08 / 1.4E-07
(1c) Mixing/Loading Wettable Powder for Aerial/Chemigation Application	0.125 (peanuts)	350	220	**36**	**2.3E-06/ 6.9E-06**	4,700	180	1.9E-07 / 5.8E-07	Not necessary		
	0.25 (sugar beets, cucurbits, celery, chinese cabbage, mustard greens)		110	**18**	**2.8E-06/ 2.8E-05 (highest crop)**	2,400	**89**	2.3E-07/ **2.3E-06**	Not necessary	3,200	9.3E-09 / 9.3E-08 (highest crop)
	0.5 (carrots, conifers, tomatoes, berries, corn)		**54**	**8.9**	**2.8E-06/ 2.8E-05 (carrots,crn) 4.7E-06/ 4.6E-05 (other crops)**	1,200	**45**	2.3-3.9E-07/ **2.3-3.8E-06**		1,600	9.3E-09 / 1.6E-07 (highest crop)
	0.75 (pome fruits, grapes)		**36**	**6**	**5.4E-06/ 5.4E-05**	780	**30**	4.6E-07/ **4.7E-06**		1,100	1.9E-08 / 1.9E-07
	0.875 (tree nuts)		**31**	**5.1**	**4.8E-06/ 4.8E-05**	670	**26**	4.1E-07/ **4.1E-06**		910	1.6E-08 / 1.6E-07
	1 (beans, mangoes, stone fruits, avocados, papayas, brassica, yams)		**27**	**4.5**	**5.5E-06/ 5.5E-05**	590	**22**	4.6E-07/ **4.6E-06**	not necessary	800	1.9E-08 / 1.9E-07 (highest crop)
	1.5 (citrus)		**18**	**3**	**5.5E-06 / 5.5E-05**	390	**15**	4.6E-07/ **4.7E-06**		530	1.9E-08 / 1.9E-07

Table 17
Benomyl: Summary of Occupational Handler Short & Intermediate-term Exposure & Cancer Risk Estimates

Exposure Scenario (Scenario #)	Application Rate (lb ai) (crops) (a)	Daily Acreage or Other Unit (b)	Baseline (c)			PPE: Single-layer Clothing + Gloves, Dust/Mist Respirator			Engineering Controls (d)		
			Dermal MOE	Inhalation MOE	Cancer Risk Private/ Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial
	0.5 (soybeans)	1200	**16**	**2.6**	**3.1E-05/ 9.4E-05**	340	**13**	**2.7E-06/ 7.7E-06**	not necessary	470	1.1E-07 / 3.2E-07
	1 (rice, wheat)		**7.9**	**1.3**	**1.3E-05/ 1.3E-04**	170	**7**	1.1E-06/ **1.1E-05**		230	4.3E-08 / 4.3E-07
(2) Applying to Orchards with an Airblast Sprayer	0.125 (bananas)	40	19,000	3,000	5.1E-08/ 5.2E-07	Not necessary			Not necessary		
	0.5 (conifers, berries)		4,900	750	5.1E-08/ 5.2E-07						
	0.75 (pome fruit, grapes)		3,200	500	6.2E-08/ 6.2E-07						
	0.875 (tree nuts)		2,800	430	5.4E-08/ 5.5E-07						
	1 (mangoes, stone fruit, avocados, papayas)		2,400	370	6.2E-08/ 6.2E-07						
	1.5 (citrus)		1,600	250	6.2E-08/ 6.2E-07						
(3) Applying with Groundboom Sprayer	0.125 (peanuts)	80	250,000	9,100	3.7E-09/ 1.1E-08	Not necessary			Not necessary		
	0.25 (sugar beets, cucurbits, celery, chinese cabbage, mustard greens)		130,000	4,500	4.5E-09/ 4.5E-08 (highest crops)						

Table 17
Benomyl: Summary of Occupational Handler Short & Intermediate-term Exposure & Cancer Risk Estimates

Exposure Scenario (Scenario #)	Application Rate (lb ai) (crops) (a)	Daily Acreage or Other Unit (b)	Baseline (c)			PPE: Single-layer Clothing + Gloves, Dust/Mist Respirator			Engineering Controls (d)		
			Dermal MOE	Inhalation MOE	Cancer Risk Private/ Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial
	0.5 (carrots, tomatoes, corn)		63,000	2,300	7.5E-09/ 7.5E-08 (highest crop)						
	1 (rice, beans, brassica, yams)		31,000	1,100	9.0E-09/ 9.0E-08 (highest crop)						
	0.5 (soybeans)	200	25,000	910	3.7E-08/ 1.1E-07						
	1 (wheat, rice)		13,000	450	1.5E-08/ 1.5E-07						
(4) Applying Sprays with a Fixed-Wing Aircraft	0.125 (peanuts)	350	See Engineering Controls [Closed Cockpit]						160,000	23,000	3.3E-09 / 9.6E-09
	0.25 (sugar beets, cucurbits, celery, chinese cabbage, mustard greens)								80,000	11,000	3.9E-09 / 3.9E-08
	0.5 (conifers, berries, carrots, tomatoes, corn)								40,000	5,600	6.6E-09 / 6.5E-08
	0.75 (pome fruit, grapes)								27,000	3,800	7.9E-09 / 7.8E-08
	0.875 (tree nuts)								23,000	3,200	6.9E-09 / 6.8E-08

Table 17
Benomyl: Summary of Occupational Handler Short & Intermediate-term Exposure & Cancer Risk Estimates

Exposure Scenario (Scenario #)	Application Rate (lb ai) (crops) (a)	Daily Acreage or Other Unit (b)	Baseline (c)			PPE: Single-layer Clothing + Gloves, Dust/Mist Respirator			Engineering Controls (d)		
			Dermal MOE	Inhalation MOE	Cancer Risk Private/ Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial
	1.0 (beans, mangoes, stone fruit, avocados, papayas, brassica, yams)								20,000	2,800	7.9E-09 / 7.8E-08
	1.5 (citrus)								13,000	1,900	7.9E-09/ 7.8E-08
	0.5 (soybeans)	1200	See Engineering Controls [Closed Cockpit]						12,000	1,600	4.5E-08 / 1.3E-07
	1 (wheat, rice)								5,800	820	1.8E-08 / 1.7E-07
(5) Applying sprays with a helicopter	No Data (see Scenario 4)										
(6a) Mixing/Loading/ Applying using a Hose-end Sprayer	0.0625/ 1,000ft2 (mushrooms)	32,000 ft2	560	3,500	7.9E-07/ **3.2E-06**	Not necessary		No Data	No Data		
(6b) Mixing/Loading/ Applying using Tank with a Hose-end Sprinkler	0.0625 / 1,000 ft2 (mushrooms)	32,000 ft2	270	Negligible	**1.7E-06/ 6.7E-06**	No Data			No Data		
(7) Mixing/Loading/ Applying as an On-Farm Seed Treatment (dry) in planter box	0.1875 lb ai/ 50 lb beans (beans, wheat, barley, oats, rye)	2	See PPE	25,000	See PPE	3,000	120,000	3.7E-08/ 3.8E-07	No Data		
		30		1,700		200	8,300	5.6E-07/ **5.6E-06**			

Table 17 Benomyl: Summary of Occupational Handler Short & Intermediate-term Exposure & Cancer Risk Estimates												
Exposure Scenario (Scenario #)	**Application Rate (lb ai) (crops) (a)**	**Daily Acreage or Other Unit (b)**	**Baseline (c)**			**PPE: Single-layer Clothing + Gloves, Dust/Mist Respirator**			**Engineering Controls (d)**		
			Dermal MOE	**Inhalation MOE**	**Cancer Risk Private/ Commercial**	**Dermal MOE**	**Inhalation MOE**	**Cancer Risk Private / Commercial**	**Dermal MOE**	**Inhalation MOE**	**Cancer Risk Private / Commercial**
(8) Mixing/Loading/ Applying as a Commercial Seed Treatment (dry) in Slurry Form	brassica, chick peas, spinach, wheat, barley, oats, rye	No Data									
(9) Mixing/Loading/ Applying as a Commercial Seedling Treatment in dry or Slurry Form (conifers)	conifers	No Data									
(10) Mixing/Loading/ Applying Solution as a Dip Treatment	avocado seeds, sweet potatoes, yams, asparagus crowns, pineapple, garlic	No Data									

Table 17
Benomyl: Summary of Occupational Handler Short & Intermediate-term Exposure & Cancer Risk Estimates

Exposure Scenario (Scenario #)	Application Rate (lb ai) (crops) (a)	Daily Acreage or Other Unit (b)	Baseline (c)			PPE: Single-layer Clothing + Gloves, Dust/Mist Respirator			Engineering Controls (d)		
			Dermal MOE	Inhalation MOE	Cancer Risk Private/ Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial	Dermal MOE	Inhalation MOE	Cancer Risk Private / Commercial
(11) Flagging Aerial Spray Application:	0.125 (peanuts)	350	73,000	4,400	9.8E-09/ 2.9E-08	Not necessary			Not necessary		
	0.25 (sugar beets, cucurbits, celery, chinese cabbage, mustard greens)		36,000	2,200	1.2E-08/ 1.2E-07 (highest crop)						
	0.5 (corn, soybeans, carrots, conifers, tomatoes, berries)		18,000	1,100	2E-08/ 2E-07 (highest crop)						
	0.75 (pome fruits, grapes)		12,000	730	2.3E-08/ 2.3E-07						
	0.875 (tree nuts)		10,000	630	2E-08/ 2.1E-07						
	1 (rice, beans, wheat, mangoes, stone fruits, avocados, papayas, brassica, yams)		9,100	550	2.3E-08/ 2.3E-07 (highest crop)						
	1.5 (citrus)		6,100	370	2.3E-08/ 2.3E-07						

(a) Lb ai/A = Pounds active ingredient/acre treated. Application rates are values found in DuPont's Benlate and Benlate SP labels, and Clean Crop's Benomyl label. The wettable powder, wettable powder in water soluble film, and dry flowable formulations are 50% active ingredient, based on the label.

(b) Daily acres treated are from the EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern.

(c) Dermal MOE = NOAEL (500 mg/kg/day) / Daily Dermal Dose (mg/kg/day); Inhalation MOE = NOAEL (0.96 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).

(d) Engineering Controls include: Water-Soluble Packets or Enclosed Cab Aircraft

Table 18
MBC Postapplication Dermal Exposure Scenarios and Risk Estimates
Based on Postapplication Day 1 and 7 DFR Data

Exposure Scenario	MBC DFR ug/cm2		Tc cm^2 / hr (b)	MOE			ED days/yr (e)	Cancer Risk: DAT 7 (f)
	DAT 1 (a)	DAT 7 (a)		Short/ Intermediate-Term (c)		Long Term (DAT 7) (d)		
				DAT 1	DAT 7			
Hand harvesting pineapple and tomato (j)	0.37-0.46	0.24-0.3	1,000	4,600-5,800	8,900-7,100	2,600-2,100	180	5.7E-7 to 7.1E-7
Irrigating,scouting peanuts, sugar beets, soybeans, wheat, barley, oats, rye (j)	0.093-0.74	0.06-0.48	1,500	1,900-15,000	3,000-24,000	NA	<15-<45	<5.3E-8 to 2.8E-7
hand harvesting, pinching, training strawberries, and blueberries (j)	0.37	0.24	1,500	3,900	5,900	1,700	180	8.5E-7
Hand harvesting low crops (celery, cucurbits, chickpeas, carrots, yams, beans, spinach) (j)	0.19-0.74	0.12-0.48	2,500	1,200-4,600	1,800-7,100	NA	30-60	1.5E-7 to 7.1E-7
Hand harvesting, hand thinning, hand pruning tree nuts (pecans, almonds, macadamia nuts, pistachio nuts) (i)	0.65-1.3	0.48-0.95	2,500	660-1,300	900-1,800	NA	60	9.4E-7 to 1.9E-6
Harvesting mushrooms (h)	0.031	0.02	2,500	28,000	43,000	12,000	250	1.6E-7
Hand harvesting pome fruits, stone fruits (i)	0.98-1.3	0.72-0.95	3,000	550-730	750-1,000	NA	45-60	1.7E-6
Harvesting berries, and brassica (j)	0.28-0.74	0.18-0.48	5,000	580-1,500	890-2,400	NA	30-60	3.5E-7 to 1.9E-6
Harvesting Grapes (g)	0.52	0.43	5,000	820	1,000	NA	75	2.9E-6
Hand harvesting citrus fruits (i)	2	1.4	8,000	140	190	NA	60	9E-6
Hand detasseling and harvesting corn (g)	0.35	0.29	17,000	360	440	NA	45	2.9E-6

* Values calculated on spreadsheet and results rounded to two significant figures
NA = Not applicable to this scenario, i.e., not a long-term activity
(a) DAT= Days after treatment; Residues reported are based on study data submitted. Harvesting values are based upon day one (DAT 1) and day 7 (DAT 7) after treatment residue values.

(b) Based upon Exposure Science Advisory Committee Policy Memo 0.003.1, August 7, 2000.

(c) Short/Intermediate Term MOE =NOAEL (10 mg/kg/day) / Absorbed daily dose. Where, ADD = absorbed daily dose =[MBC residue ($\mu g/cm^2$) * Tc (cm^2 /hr) * mg/1,000 ug * 8 hrs/day * dermal absorption factor (0.035)] / body weight [60 kg for all time periods except 70 kg for long-term.]

(d) MBC Long-Term MOE = MBC chronic NOAEL (2.5 mg/kg/day) / Absorbed daily dose

(e) ED = Exposure duration = days performing work per year

(f) Cancer Risk = MBC LADD * Q_1* [0.00239 $(mg/kg/day)^{-1}$], where, LADD = lifetime absorbed daily dose = (mg/kg/day) = absorbed daily dose (mg/kg/day) * ED (days/year) * 35 years] / [70 years * 365 days/year].

(g) Grape DFR data used (application rate of 0.75 lb ai/are, single application); adjusted to account for different allowable application rates for different crops.

(h) Mushroom DFR data based on an extrapolation of the exposure study data from postapplication day 17 to day 1 using regression exposure data (ug/hr) from study were divided by TC of 2,500 cm2/hr to obtain DFR in ug/cm2.

(i) Apple DFR data used (application rate of 0.75 lb ai/are, single application); adjusted to account for different allowable application rates for different crops.

(j) Strawberry DFR data used (application rate of 0.5 lb ai/are, seven applications); adjusted to account for different allowable application rates for different crops.

8.0 INCIDENTS

A number of incidents have been associated with benomyl. A detailed summary of these incidents is provided in the attached memorandum from J. Blondell and M. Spann to G. Bangs, D229878, October 26, 1999. Based on the California Department of Pesticide Regulation 1982-1993 data, the majority of benomyl incidents involved skin illnesses such as rashes and contact dermatitis that resulted in medical attention. (It should be noted that in animals, benomyl is a mild to moderate dermal sensitizer). About two-thirds of these cases occurred in workers who had direct contact from handling benomyl. Exposure to field residue was also a significant source of adverse effects, although is should be noted that most of these cases resulted from intensive contact with treated foliage. Poison Control Center data from 1993-1996 also show that dermal and ocular effects were the most common effect reported, and therefore tend to support the California data. Prior to 1991, there were several undocumented or poorly documented reports of workers and other bystanders being exposed to spray drift. Benomyl was ranked 42nd of the National Pesticide Telecommunications Network list (NPTN) of 200 chemicals with the most calls from 1984-1991 with 90 human incidents and 6 animal (pet) incidents.

9.0 DEFICIENCIES / DATA NEEDS (CONFIRMATORY DATA)

Additional data requirements have been identified in the attached Science Chapters and are summarized here.

Toxicology Data for OPPTS Guideline:

The Hazard Identification Assessment Review Committee (HIARC) has requested a developmental neurotoxicity (DNT) study in rats for benomyl. Toxicology data for carbendazim (Methyl 2-Benzimidazole Carbamate) or MBC, the primary environmental breakdown product of benomyl, are also considered in this assessment, and are incomplete. The HIARC requested two toxicity studies with MBC, a 21 day dermal toxicity study in rats and a developmental neurotoxicity study in rats. In addition, the 2-generation rat reproduction and subchronic studies for MBC fail to meet the Subdivision F Guidelines.

Product and Residue Chemistry Data for OPPTS Guidelines

Product Chemistry. All pertinent data requirements are satisfied for the du Pont benomyl TGAI; however, additional data are required for GLN 830.7050 (UV/Visible Absorption) and GLN 830.1800 (Enforcement Analytical Methods) for the 95% T. Provided that the registrant either certifies that the suppliers of beginning materials and the manufacturing process for the benomyl T have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of benomyl with respect to product chemistry data requirements.

Residue Chemistry. The following confirmatory data requirements remain outstanding or are now required:

(a) The labels for the 50% WP formulation should specify sweet corn in the list of "Crops Grown for Seed" permitted in California, and limit use on papayas to Florida. Current Agency policy does not allow feeding restrictions for cereal grain forages, therefore, restrictions prohibiting the grazing of livestock in treated field or on plants grown from treated seeds must be deleted. The following statement should appear on all benomyl EPs: "Do not rotate to crops other than those that appear on this label." The absence of a rotational crop restriction as above on the labels will result in a requirement for limited and/or full field rotational crop residue studies.

(b) A HPLC method is listed (Method II, PAM) for analysis of residues of benomyl and its metabolites MBC, 4-HBC, and 5-HBC in/on plant commodities and in animal commodities. Method II does not describe the determination of metabolite 2-AB, which is a residue to be regulated in plant commodities as a result of the recent HED Metabolism Committee deliberations. The PAM method does not adequately recover 2-AB (radioactive) from soybeans. A revised residue method (the ethanol:detergent method) recovered 84% 2-AB from soybeans; this method should undergo an independent laboratory validation (soybeans and rice grain) and an Agency method try out for use as an enforcement method. Also, multiresidue data for 2-AB, 4-HBC and 5-HBC must be submitted.

(c) The requirements for storage stability data are not considered fulfilled for reregistration purposes. Storage stability data are still required to support established tolerances in plant and animal commodities. Information on sample storage intervals and conditions are still required for peanuts. The registrant should recognize that residue studies that are incomplete with respect to sample handling and storage information may have to be repeated.

(d) Additional residue data are required for apricots, nectarines, carrots, canola, corn (sweet), collards, mustard greens, rice, and spinach. Because the grazing restrictions for barley, oats, rye, and wheat must be removed from EP labels, tolerances are required for barley forage, oat forage, rye forage, and wheat forage. The proposed tolerances must be supported by appropriate residue data.

Occupational Exposure Data for OPPTS Guidelines

There are insufficient data to assess the commercial seed/seedling treatment uses, or dip treatments, and additional data are requested to support these uses.

10.0 REFERENCES

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Wood et al. 1982. Chronic feeding study in CD-1 mice (2 yrs). MRID # 256028, and 256029

APPENDIX A
SUMMARY OF TOXICOLOGICAL DATA FOR BENOMYL AND MBC

Table A-1. Toxicity Studies for Benomyl		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3100 (82-1(a)) Subchronic Feeding in Rats (90 days)	00066771 (1967) unacceptable guideline M: 0, 9, 45, or 214 F: 0, 9, 46, or 234 (0, 100, 500 or 2500 ppm)	72% a.i. benomyl NOAEL: 45 (M), 46 (F) LOAEL: 214 (M), 234 (F) based on increases in SGPT in males and increased relative and absolute liver weights in females
NA Subchronic (28 day) Oral in Male CD-1 Mice	41607903 (1990) Supplementary, not conducted to satisfy guidelines 0, 15.7, 85.4, 586 or 1180 (0, 100, 500, 3750 or 7500 ppm) (males only)	96.1% a.i. benomyl NOAEL: 85.4 LOAEL: 586 based on an increase in relative and absolute liver weights, an increase in the incidence of cellular hypertrophy and increased cell proliferation.
870.3150 (82-1(b)) 90 Day Oral (Diet) in Dogs	00066785 (1968) Unacceptable guideline. Two chronic studies exist that would supercede this data requirement 0, 2.5, 12.5 or 62.5 (0, 100, 500 or 2500 ppm)	51% a.i. benomyl NOAEL:12.5 LOAEL: 62.5 based on increased SGPT, alkaline phosphatase and albumin:globulin ratio in males
870.3200 (82-2) 21-Day Dermal Toxicity Study in Rabbits	00097287 (Hood et al. 1969) Acceptable guideline 0, 50, 250, 500, 1000 and 5000 (Doses already adjusted for % a.i. in study)	53% a.i benomyl NOAEL: 500 LOAEL: 1000 based on 30% and 24% decreases in testicular weight and testes-to-body weight ratios, respectively in males and diarrhea, oliguria and hematuria in females. Moderate skin irritation was reported for all dose groups.
870.3465 (82-4) Subchronic Inhalation in Sprague-Dawley Rats (90 days)	40399501 (Warheit 1987) Acceptable guideline M: 0.96, 4.8 or 19.2 mg/kg/day F: 1.4, 7.0 or 28.8 mg/kg/day (0, 10, 50 or 200 mg/m^3, or 0, 0.01, 0.05 or 0.2 mg/L) 4 hr/day	**95% a.i. benomyl** NOAEL: 0.96 (males) LOAEL: 4.8 (males) basesd on olfactory degeneration was characterized by necrosis, chronic and acute inflammation and loss of olfactory epithelium with foci of repair.
870.4100 870.4200a (83-1(a) 83-2) Chronic feeding study in CD rats	MRID : 00066772 Accession # 091561B Sherman et al. 1969 Minimum 0, 5, 25, or 125 (0, 100, 500 or 2500 ppm) (Doses adjusted for % a.i.)	**51 or 72.2% a.i. benomyl** NOAEL: >125 (HDT) LOAEL: none established Deficiencies: Limited clinical chemistry analysis, and only 36 rats/sex/dose were evaluated when 50/rats/sex/dose required.
870.4100 (83-1b) Chronic feeding study in beagle dogs (2 yrs)	00066786, 00061618, 00081913, 00097305, 00097318, 00097326 Sherman et al. 1968, 1970, Lee 1970, 1971 and 1977 Acceptable guideline 0, 2.5, 12.5, or 62.5 (0, 100, 500 and 2500 ppm) (Doses adjusted for % a.i.)	**50% a.i. benomyl** NOAEL: 12.5 LOAEL: 62.5 (HDT) based on liver and testicular effects and decreased weight gain and food consumption.
870.4200b (83-2b) Chronic feeding study in CD-1 mice (2 yrs)	00096514 Schneider et al. 1982 Acceptable guideline 0, 75, 225 or 1125 (750) (0, 500, 1500 and 7500 ppm) (the 7500 ppm dose level was reduced to 5000 ppm after week 37).	**99, 99.2% a.i. benomyl** NOAEL: none LOAEL: 75 based on significant increase in hepatocellular carcinomas in both males and females, and increase in combined incidence of hepatocellular adenomas and carcinomas in mid and high dose females. Testicular degeneration at the highest dose tested.

Table A-1. Toxicity Studies for Benomyl		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3700a (83-3a) Developmental Study in CHR:CR rats (gavage)	00148393 (Accession # 256575) (Staples and Aftosmis 1980) Acceptable guideline when considered with MRID # 00115674, 00126522 (below) 0, 15.6, 31.2, 62.5 or 125 (gestation day 7-16)	**99% a.i. benomyl** Maternal NOAEL: 125 Maternal LOAEL: None Developmental NOAEL:31.2 Developmental LOAEL: 62.5 based on a significant increase in fetal and litter incidence of ocular malformations, specifically, microphthalmia and anophthalmia and decreased fetal weight. At 125 mg/kg, an increased incidence of malformations of the brain, characterized by distended lateral ventricles and hydrocephaly was noted.
870.3700a (83-3a) Developmental Study in CHR:CR rats (gavage)	00115674, 00126522 (Staples 1982) Acceptable when considered with MRID 00148393 (above) 0, 3, 6.25, 10, 20, 30 or 62.5 mg/kg (gestation day 7-16)	**99.1% a.i. benomyl** Maternal NOAEL: 62.5 Maternal LOAEL: None Developmental NOAEL: 30 Developmental LOAEL: 62.5 based on microphthalmia
870.3700a (83-3a) Developmental Study in Wistar rats (gavage)	41051521 Kavlock et al. 1982 Literature Study 0, 15.6, 31.2, 62.5 or 125 mg/kg (gestation day 7-16)	**% a.i. benomyl not given (technical)** Maternal NOAEL: 125 (HDT) Maternal LOAEL: none Developmental NOAEL: 31.2 Developmental LOAEL: 62.5 based on the increased incidence of microphthalmia, increased fetal mortality reduced fetal weight, and delayed skeletal and visceral maturation.
870.3700a (83-3a) Developmental Study in Wistar rats (diet)	41051521 Kavlock et al. 1982 Literature Study 0, 169, 298, 505 (approximately 0, 1690, 3380, and 6760 ppm) (gestation day 7-16)	**% a.i. benomyl not given (technical)** Maternal NOAEL: 298 Maternal LOAEL: 505 (reduced weight gain) Developmental NOAEL: 169 Developmental LOAEL: 298 based on weight decreases in fetuses and enlarged renal pelves.
Postnatal Study in Wistar rats (gavage)	41051521 Kavlock et al. 1982 Literature Study 0, 15.6, or 31.2 mg/kg (gestation day 7 through lactation day 15)	**% a.i. benomyl not given (technical)** Maternal NOAEL: 31.2 (HDT) Maternal LOAEL: none Developmental NOAEL: 15.6 Developmental LOAEL: 31.2 based on decreased weight of testes, ventral prostate and seminal vesicles.
870.3700a (83-3a) Developmental Study in CD-1 Mice (gavage)	41051521 Kavlock et al. 1982 Literature Study 0, 50, 100, or 200 mg/kg (gestation day 7-17)	**% a.i. benomyl not given (technical)** Maternal NOAEL: 200 (HDT) Maternal LOAEL: none Developmental NOAEL: 50 Developmental LOAEL: 100 based on supra occipital scars, subnormal vertebral centrum, supernumerary ribs and cleft palate.

Table A-1. Toxicity Studies for Benomyl		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3700b (83-3b) Developmental Study in Hra (New Zealand White) SPF rabbits (gavage)	43788301 (1995) Acceptable guideline 0, 15, 30, 90 or 180 mg/kg (gestation day 7-28)	**97.4% a.i. benomyl (DPXT-1991-529)** Maternal NOAEL: 90 Maternal LOAEL: 180 clinical signs of toxicity (stained tails and reduced feed consumption) Developmental NOAEL (systemic):180 Developmental LOAEL(systemic): none established
870.3800 (83-4) 2-Generation Reproduction Toxicity in Crl:CDBR Rats (diet)	41887901 (1991) Acceptable guideline P1 Males: 0, 5, 28, 168 and 553 mg/kg P1 Females: 0, 7, 35, 210 and 712 mg/kg F1 Males: 0, 8, 38, 234 and 954 mg/kg F1 Females: 0, 9, 47, 280 and 1,168 mg/kg (0, 100, 500, 3000 and 10,000 ppm)	**99% a.i. benomyl (DPX-T1991-529)** Parental NOAEL: 28 (M), 35 (F) (500 ppm) Parental LOAEL: 168 (M), 210 (F) (3000 ppm) Reproductive NOAEL: 28-47 (500 ppm) Reproductive LOAEL: 168-280 (3000 ppm) Effects: At 3000 ppm there were decreases in the body weights of F2a and F2b offspring on days 14 and 21 of lactation, decreases in sperm counts reported for F1 parental males, and testicular pathology (atrophy, degeneration of the seminiferous tubules) in both generations. At 10,000 ppm oligospermia in addition to statistically significant decreases in the birth and lactation weights of F1, F2a and F2b pups, decreased testicular weights in P1 and F1 males and decreases in body weights, body weight gains and food consumption in parental animals. In the F2b offspring, there was an increase in the number of pups with partially opened or unopened eyes and a nonsignificant decrease in pup survival.
NA Single oral dose (gavage) study	Hess et al. 1991 0, 25, 50, 100, 200, 400 or 800 mg/kg	NOAEL: none observed LOAEL: 25 based on biologically significant premature release of germ cells and occlusions of the efferent ductules of the testes.
870.1300 Rat inhalation study (nose-only)	00097281 Hornberger 1969 0, 7.5, 33 mg/kg (0, 0.2, 0.82 mg/L)	NOAEL: 7.5 LOAEL: 33 based on decreased spermatogenesis.
Acute dog inhalation study	00097282 Littlefield 1969 0, 32, or 82 mg/kg (0, 0.65 or 1.65 mg/L)	NOAEL: 32 LOAEL: 82 based on decreased spermatogenesis.
870.6100a (81-7) Delayed Neurotoxicity Study in Hens	241930 (1979) Not acceptable guideline 0, 500, 2500 or 5000	**% a.i. benomyl not given** NOAEL: 2500 LOAEL: 5000 based on decreased activity; No delayed neurotoxicity Note: 5/10 hens exposed to 5000 mg/kg died between 6-9 days of treatment.
870.6200a (81-8) Acute Neurotoxicity Study in Crl:CDBR Rats	42817003 (1993) Acceptable guideline 0, 500, 1000 or 2000	**97.4% a.i. benomyl (DPX-T1991-529)** NOAEL (systemic): 2000 LOAEL (systemic): none established Effects: No signs of neurotoxicity observed, Testicular lesions were observed at 500 and 1000 mg/kg.

Table A-1. Toxicity Studies for Benomyl		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.6200a (82-8) 13 Week Rat (Sprague-Dawley) Neurotoxicity Study	43277901 (1994) Acceptable guideline M: 0, 6, 158, or 456 F: 0, 8, 199 or 578 (0, 100, 2500 or 7500 ppm)	**97.4% a.i. benomyl (DPX-T1991-529)** NOAEL (systemic): 158 (M), 199(F) LOAEL (systemic): 456 (M), 578 (F) based on increased motor activity and decreased terminal body weight (15% males and 12% females) and decreased body weight gain (approximately 25% for both sexes). Benomyl was not considered neurotoxic because the increased motor activity occurred in the presence of systemic toxicity.

(1) Unless specified, mg ai benomyl/kg/day.
NOAEL = No Observable Adverse Effect Level
LOAEL = Lowest Observable Adverse Effect Level
SGPT = Serum Glutamic Pyruvic Transaminase
NA = Not applicable

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3150 (82-1(b)) Subchronic Feeding in Dogs (90 days)	00099130 Sherman et al. 1970 Unacceptable guideline M: 0, 2.7, 14.4, or 40.7 F: 0, 2.7, 11.3, or 35 (0, 100, 500 or 1500/2500 ppm)	**53% a.i. carbendazim** NOAEL: 11.3 (F), 14.4 (M) LOAEL: 35 (F), 40.7 (M) based on histopathology changes in liver (1/4 males and 1/4 females) and testes (1/4 males) and increased alkaline phosphatase, cholesterol and SGPT. Liver effects included hepatic cirrhosis (hepatic cell necrosis, tubular collapse, and increased fibrous connective tissue around triads). Decreased testes weight in 3/4 males in the high dose.
870.4100 870.4200 (83-1& 2) Chronic feeding/ carcinogenicity study in CD rats (2 yrs)	00088333, 00068982, Accession #: 2328700, 232871 Sherman et al. 1972, Lee 1978 Minimum 0, 5, 25, 250 or 125/500 (430) [0, 100, 500, 5000 or 2500/10000 (8557) ppm]	**53% a.i. carbendazim** NOAEL:25 LOAEL: 250 based on statistically significant decreases in red blood cell parameters (hematocrit, hemoglobin an red blood cells) in females and histological lesions in the liver (cholangiohepatitis and pericholangitis) in males and females. No evidence of carcinogenicity. Deficiencies: Only 36 rats/sex/dose tested (only 20 rats/sex were in 250 mg/kg/day dose group). Lack of complete clinical chemistry data and histopathology examination. At 24 months, only liver evaluated in 5 and 25 mg/kg/day groups and only liver, kidney and testes evaluated in 250 mg/kg/day group.
870.4100b (83-1b) Chronic feeding study in beagle dogs (2 yrs)	00088333 Accession #: 232870-0, 232871 (Sherman et al. 1972) Acceptable guideline 0, 2.5, 12.5, or 37.5/62.5 (0, 100, 500 and 1500/2500 ppm) (Doses adjusted for % a.i.)	**53% a.i. carbendazim** NOAEL: 2.5 LOAEL: 12.5 based on swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis and biochemical alterations indicative of liver damage (i.e., increased cholesterol, total protein, SGPT and alkaline phosphatase levels, and decreased A/G ratio). At 37.5/62.5 mg/kg/day, anorexia, distended abdomens and poor nutritional condition were reported.
870.4100b (83-1b) Chronic feeding study in beagle dogs (1 yr)	00164304 Accession # 265664 (Stadler et al. 1986) Acceptable guideline F:0, 2.93, 6.43 or 16.54 mg/kg M: 0, 3.2, 7.19, 17.07 (0, 100, 200, or 500 ppm)	**98.8% a.i. carbendazim** NOAEL: 6.43 (200 ppm) LOAEL: 16.54 (500 ppm) based on possible transient increase in cholesterol (males and females) consistent with previous dog feeding studies.
870.4200b (83-2b), 83-1 Chronic feeding study in CD-1 mice (2 yrs)	00096513, 00154676 256028, and 256029 Wood et al. 1982, Schneider, Wood and Hall 1982 Core Grade: acceptable guideline. The study was designed to specifically evaluate the liver carcinogenicity potential of MBC 0, 75, 225, 1125 (females) or 1125/563 (males) (0, 500, 1500 or 7500 (females) or 7500/3750 (males) ppm)	**99.3% a.i. carbendazim** NOAEL (non-cancer systemic): 75 LOAEL (non-cancer systemic): 225 based on liver toxicity (hepatocellular necrosis and swelling), body weight decrease and lymphoid depletion. In both sexes, there was an increased incidence of liver tumors. In males, hepatocellular carcinomas were noted at 225 mg/kg/day, while females exhibited carcinomas and adenomas at all dose levels. Note: The 7500 ppm was reduced to 3750 ppm at 66 weeks in males due to increased mortality.

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.4200b (83-2b) Chronic feeding/ carcinogenicity study in NMRKf mice (2 years)	00154679 Accession # 2560302 (Donaubauer et al. 1982) Unacceptable guideline 0; 5.8-7.1; 17.1 -21.2; 34.4 - 41.9 or 522 - 648 (0, 50, 150, 300 or 1000/5000 ppm).	**99% a.i. carbendazim** NOAEL (non-cancer systemic): 34.4 - 41.9 LOAEL (non-cancer systemic): 522 - 648 based on increases the incidences of hepatic cell hypertrophy, clear cell foci and hepatocellular necrosis. No increased incidence of carcinogenicity was noted. Deficiencies: incomplete examination of most recommended tissues, blood and urine were not collected for analysis.
870.4200b (83-2) Chronic feeding/ carcinogenicity study in Swiss mice (80 weeks)	00153420 Accession # 256029 (Beems et al. 1976) Unacceptable guideline 0, 22.5, 45 or 750 (0, 150, 300 or 5000 ppm)	**99% a.i. carbendazim** NOAEL:45 LOAEL:750 based on hepatic alterations which included increased relative liver weights in both sexes, increased number of foci of cellular alterations in the liver in females, neoplastic nodules in females and hepatoblastomas in males Deficiencies: Brief methods, there were no historical data or microscopic or gross pathology reports for individual animals, and there was no assurance that the diets were analyzed for compound homogeneity and stability. In addition, there were no hematology or clinical chemistry analysis, nor urinalysis. Only organs or lesions suspected of being tumors and livers (2 sections) were examined histologically.
870.3700a (83-3a) Developmental Study in Crl:CE BR rats (gavage)	40438001 Alvarez 1987 Acceptable guideline 0, 10, 20, 90 gestation day 7-16	**98.8% a.i. carbendazim** Maternal NOAEL: 20 Maternal LOAEL:90 (increased absolute liver weight) Developmental NOAEL:10 Developmental LOAEL: 20 based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations.
870.3700b (83-3b) Developmental Study in New Zealand White Rabbits (gavage)	Accession # 260571 (Christian et al. 1985) Acceptable guideline 0, 10, 20 or 125 gestation day 7-19	**98.7% a.i. carbendazim** Maternal NOAEL: 20 Maternal LOAEL:125 (abortions and decreased body weight) Developmental NOAEL:10 Developmental LOAEL: 20 mg/kg/day based on decreased implantations and litter size, and increased resorptions. Malformations (fused ribs, and malformed cervical vertebrae) were noted at 125 mg/kg/day
870.3800 (83-4) Reproductive Study in ChR-CD rats (diet)	00088333 Sherman et al. 1972 Unacceptable guideline 0, 5, 25, 250 or 125/500 (0, 100, 500, 5000 or 2500/10,000 ppm)	**50 or 70% a.i. carbendazim** Reproductive NOAEL:25 Reproductive LOAEL: 250 based on toxic signs of decreased pup weight noted at weaning. Deficiencies: Litter (or fetal) weights were not measured at birth, therefore it is impossible to attribute weight decrease in 5000 and 2500/10000 ppm groups to prenatal or lactation period. Only 16 dams (20 dams for 5000 ppm), resulting in 10-16 litters per group were available, rather than the 20 litters recommended in the guideline. There was no special attention for the testes, a known target organ, including organ weights measurements.

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
NA Single dose (gavage) rat study	Nakai et al. (1982) Literature Study 0, 50, 100, 200, 400 or 800 mg/kg	NOAEL: none observed LOAEL: 50 based on premature release of immature germ cells 2 days post exposure, and atrophy of a few seminiferous tubules and significant decrease in seminiferous tubule diameter 70 days post exposure

(1) Unless specified, mg ai MBC/kg/day.
NOAEL = No Observable Adverse Effect Level
LOAEL = Lowest Observable Adverse Effect Level

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