Benomyl
Position Document 2/3

Special Pesticide Review Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Benomyl: Position Document 2/3

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I. Introduction

Benomyl belongs to the benzimidazole class of fungicides. It is a broad-spectrum systemic fungicide used mainly as a 50 percent wettable powder which is mixed with water for application. Approximately 3 million pounds are currently used on 43 food crops and 41 ornamentals annually. Additional background information was presented in the Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing Benomyl (EPA, 1977).

A. Background

1. The Statute

The Federal Insecticide, Fungicide, and Rodenticide Act, as amended (FIFRA)(7 U.S.C. 136 et seq.) regulates all pesticide products. Section 3(a) of FIFRA requires all pesticide products to be registered by the Administrator before they may be sold or distributed. Before the Administrator may register a pesticide, however, he must determine that its use will not result in "unreasonable adverse effects on the environment" [Section 3(c)(5)(D)], which is defined by section 2(bb) of FIFRA to mean "any unreasonable adverse effects to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide." In other words, any registration decision must take into account both the risks and the benefits from the use of the pesticide.

Section 6(b) of FIFRA authorizes the Administrator to issue a notice of intent to cancel the registration of a pesticide or to change its classification if it appears to him that the pesticide or its labeling "does not comply with the provisions of [FIFRA] or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." Thus the Administrator must cancel the registration of a pesticide whenever he determines that it no longer satisfies the statutory standard for registration which requires, among other things, that the pesticide not cause "unreasonable adverse effects on the environment" [Section 3(c)(5)]. He may also cancel the registration of a pesticide if its labeling does not comply with the misbranding provisions of FIFRA which require the labeling to contain language "adequate to protect health and the environment"[FIFRA 2(q)].

2. The "RPAR" Process

The Agency has designed a public process to gather risk and benefit information about a suspect pesticide so that the Administrator may make a balanced decision concerning it. This process is known as the Rebuttable Presumption Against Registration (RPAR) process; it is set out in the Code of Federal Regulation (CFR) Title 40 Section 162.11.

In broad summary, these regulations describe the various criteria for the determination of unreasonable adverse effects, and provide that a RPAR shall arise if the Agency determines that any of these criteria have been met. Once the Agency issues such a rebuttable presumption, the regulations provide an opportunity for registrants, applicants, and interested persons to submit evidence to rebut the presumption. These persons may also submit evidence relating to the economic, social, and environmental benefits of any use of the pesticide. If the presumptions of risk are not rebutted, the evidence on the benefits of the pesticide is then evaluated and considered along with the information on the risks from the pesticide. The Agency then analyzes various methods of reducing the amount of risk from the pesticide together with their costs and determines whether it can regulate the pesticide in such a manner so as to strike the balance between risks and benefits. Striking the balance may necessitate cancelling certain uses of the pesticide.

3. Organization of Position Document 2/3

This Position Document contains five parts. Part I is the introductory section. Part II contains an evaluation of the risks associated with benomyl. It includes the Agency's original RPAR decision, descriptions of relevant experiments and field observations, Agency responses to RPAR rebuttal comments, and the Agency's assessment of those

risks in light of the comments received. Part III describes the process which the Agency employed to gather and to analyze use-specific information about the economic benefits associated with benomyl. Part IV delineates the range of regulatory options available to the Agency for the reduction of unreasonable adverse effects, and explains the basis of the Agency's selection of alternative courses of action for each registered use of benomyl. Part V sets forth the Agency's evaluation of the risks and benefits associated with each use of benomyl and the Agency's evaluation of each available regulatory option. The beneficial and adverse impacts for each alternative course of action are evaluated, and the rationale for the decision on each use is set forth.

B. Basis of the Rebuttable Presumption

1. Acute Toxicity: Hazard to Wildlife, Aquatic Species

40 CFR Section 162.11 (a)(3)(i)(B)(3) provides that a rebuttable presumption shall arise if use of a pesticide results in a maximum calculated concentration after direct application to a 6-inch layer of water which is more that one-half the acute LC_{50} for aquatic organisms representative of the organisms likely to be exposed as measured on test animals specified in the Registration Guidelines.

The calculated concentration of benomyl in water (0.734 ppm) after its direct application to rice according to label directions is greater than one-half the LC_{50} for bluegill, channel catfish, and Daphnia magna. Accordingly, the Agency issued a presumption against all registrations and applications for registration of pesticide products containing benomyl which are for direct application to water (EPA, 1977).

2. Mutagenic Effects in Multitest Systems

40 CFR Section 162.11 (a)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide's ingredients, metabolites, or degradation products induce mutagenic effects, as determined by multitest evidence. In Position Document 1, the Agency cited studies which show that benomyl and its metabolite, MBC, produce somatic chromosomal abnormalities, spindle-effects, and point (gene) mutations in microbial and mammalian test systems and studies which show that these compounds cause mutagenic effects in plants. The Agency concluded that benomyl and MBC are mutagenic and issued a RPAR against all pesticide products containing benomyl (EPA, 1977).

3. Other Chronic or Delayed Toxic Effects

40 CFR Section 162.11 (a)(3)(ii)(B) provides that a rebuttable presumption shall arise if a pesticide causes any other chronic or delayed toxic effect in test

animals at a dosage that is substantially higher than that to which humans can reasonably be anticipated to be exposed when ample margins of safety are taken into account (EPA, 1977).

a. Teratogenic Effects

In Position Document 1, the Agency cited a study by Schentenberg and Torchinski (1972), which reported teratogenic effects when benomyl was orally administered (in vegetable oil) to Wistar rats in doses up to 125 mg/kg/day from day 1 to 20 or from day 7 to 15 of gestation. Torchinski (1973) later induced teratogenic effects in Wistar rats by administering benomyl (145 mg/kg) by gavage on day 12 of gestation. The Agency did not presume against benomyl on the basis of teratogenicity from dietary exposure because the anticipated exposure from food intake alone is sufficiently low that an adequate margin of safety exists for the teratogenic effects observed in the Schentenberg and Torchinski study.

However, the Agency concluded that the amount of benomyl to which women of childbearing age might be exposed is too high relative to the dose which has produced teratogenic effects in animals. This conclusion was based on the Agency's finding that the amount of benomyl absorbed dermally during home garden use would not provide an adequate margin of safety relative to the no-observable-effect level observed in the Schentenberg and Torchinski

study. The Agency also noted that a person might be exposed to additional amounts of benomyl through inhalation or ingestion. Therefore, the Agency concluded that all home use pesticide products containing benomyl resulted in an unacceptable risk of teratogenic effects and the Agency issued a presumption against registration for all home use products (EPA, 1977).

b. Reduction in Spermatogenic Activity

In Position Document 1, the Agency cited acute and subacute oral studies which identify the testes as a primary target of benomyl. It also cited inhalation toxicity studies which showed a reduction in the spermatogenic activity of rats and dogs which are exposed to concentrations of benomyl of 33 mg/kg and 82 mg/kg, respectively. In these studies no effects were observed at concentrations of 7.5 mg/kg in rats and 32 mg/kg in dogs. In Position Document 1, the Agency concluded that current uses of benomyl would not result in residues of benomyl on food crops which would pose an unreasonable risk of reduction in spermatogenic activity. However, applicators would be exposed to much higher concentrations of benomyl than the general public. The Agency concluded that there was not an adequate margin of safety between the concentration of benomyl which an applicator might inhale during 4 hours of spraying and the dose which had produced a decrease

in spermatogenic activity in animals. Accordingly, the Agency issued a RPAR against all pesticide products containing benomyl (EPA, 1977)

4. Population Reductions in Nontarget Organisms

40 CFR section 162.11 (a)(3)(ii)(C) provides that a rebuttable presumption shall arise if a pesticide can reasonably be anticipated to significantly reduce local, regional, or national populations of nontarget organisms.

In Position Document 1 the Agency evaluated several studies which indicate that benomyl is highly toxic to earthworms. In studies by Stringer and Wright (1973) earthworm populations were "virtually eliminated" in apple orchard plots sprayed with benomyl. Stringer and Lyons (1974) reported that the spraying of benomyl in orchards reduced not only the number and biomass of all earthworm species combined, but also those of each individual species. Tomlin and Gore (1974) applied benomyl to pastures and reduced earthworm populations by over 90 percent. Black and Neely (1975) found that injection of benomyl into the soil at a rate of 36 g/m^2 reduced the populations of earthworms by 80 percent. The Agency concluded that the use of benomyl according to current label directions can reasonably be expected to result in significant reductions in local populations of earthworms. Accordingly, the Agency issued a RPAR against pesticide products containing benomyl which are registered for outdoor use (EPA, 1977).

II. Risk Analysis and Assessment

A. Rebuttal Analysis

The Agency has received comments concerning the effects which were the basis for the RPAR, namely, (1) acute toxicity to aquatic organisms, (2) mutagenic effects, (3) reproductive effects, and (4) reduction of earthworm populations. The Agency has reviewed the available studies again in light of the rebuttal comments and has concluded that comments addressing the acute toxicity to aquatic organisms fail to rebut the presumptions and that benomyl continues to exceed the risk criteria outlined in 40 CFR Section 162.11 for this effect. The rebuttal comments on mutagenic effects support the Agency's position that benomyl or its metabolite, MBC, is a spindle poison which interferes with proper chromosome segregation during mitosis resulting in non-disjunction. Although benomyl has been shown to function as a weak point mutagen in bacterial systems, there is insufficient evidence currently available to sustain the presumption that benomyl is a point mutagen in mammalian systems. On the basis of additional information submitted in rebuttal, the Agency has revised the estimation of human exposure and has concluded that the presumption based on reduction in spermatogenic activity has been rebutted for all uses except aerial application. Rebuttal comments questioned the adequacy of the teratology study on

which the presumption was based. The Agency concluded that sufficient doubt was raised about the study to require an attempt at replication. Preliminary results from the new teratology study identify benomyl as a teratogen but do not establish a no-observable-effect level (NOEL) (Kavlock, 1978). The rebuttal comments provide evidence that significant local reductions in populations of earthworms would not occur from the use of benomyl. The Agency has concluded that the non-target organism presumption has been rebutted.

1. Rebuttals Relating to the Presumption of Acute Toxicity: Hazard to Wildlife, Aquatic Species

The Agency calculated that application of benomyl at a rate of up to 2 lb/acre according to the label directions for use against rice blast and stem rot results in a concentration of 734 ppb in a 6-inch layer of water. This concentration is greater than one-half the acute LC_{50} for bluegill, channel catfish, and Daphnia magna (Table II-1) (EPA, 1977).

The Agency received comments on the presumption that benomyl presents a hazard of acute toxicity to aquatic organisms. The Agency has evaluated the rebuttal comments and the additional information submitted and has concluded that these rebuttals do not successfully rebut the presumption that benomyl presents a hazard of acute toxicity to aquatic species.

Table II-1. The 96-hour LC_{50} for Bluegill Sunfish and Channel Catfish and the 48-hourd LC_{50} for *Daphnia magna*

Organism	LC_{50}	Source
Bluegill sunfish	1.2 pm	McCann (1973)
Bluegill sunfish	2.6 ppm	Knott (1968)
Bluegill sunfish	0.2 ppm	McCann (1977)
Bluegill sunfish	0.4-0.5 ppm	McCann (1977)
Channel catfish		
Yolk sac	8-10 ppb	Finley (1977)
6-Day-old fry	12 ppb	Finley (1977)
12-Day-old fry	10 ppb	Finley (1977)
Daphnia magna	0.64 ppm *	Canton (1976)

* 48-hour LC_{50} value

a. Lack of Exposure Following Application on Rice

DuPont [30000/23:1296] contended that the Agency's presumption does not conform to the provisions of 40 CFR because benomyl is not registered for any uses involving its direct application to water. They further stated that no aquatic organisms are exposed to benomyl after its application on rice.

The Agency rejects this rebuttal. The Agency has issued a registration for the application of benomyl on rice while the rice is growing in a permanent flood of about 4 to 6 inches of water. In monitoring studies of rice fields, residues of benomyl of up to 3800 ppb in mud and 90 ppb in the water were found. Therefore, the benomyl applied to rice plants must have reached the water in the rice field. DuPont does not supply any evidence in the rebuttal to support their contention that no aquatic organisms are exposed to benomyl following its application on rice. On the contrary, field monitoring studies performed by duPont demonstrated that water containing toxic levels of benomyl (20 to 50 ppb) is drained from rice fields into natural bodies of water which contain aquatic organisms (Leitzke, 1978a).

b. Lack of Significant Adverse Effects

DuPont [30000/23:1296] contended that the anticipated exposure to local, regional, or national populations of nontarget organisms to benomyl is not likely

to result in any significant adverse effects on these organisms when it is used according to the directions and restrictions on the label.

The Agency rejects this rebuttal contention because the available evidence indicates that adverse effects on aquatic species have resulted. For example, the rebuttor noted in a letter from Glen Whitney, a plant pathologist [30000/23:1296] that water from the fields where users have sprayed benomyl can and does kill catfish. The rebuttor also conceded that there are five reports in their own complaint files which associate the use of benomyl with adverse effects on fish. Two of these reports involved catfish kills which allegedly occurred when water from a rice field treated with benomyl drained into an adjacent catfish pond (Leitzke, 1978a).

c. Lack of Fish Kills When Label Directions Followed

DuPont [30000/23:1296] contended that their files and those of EPA show that no fish kills have resulted from the use of benomyl when users followed the directions on the label.

The Agency rejects this rebuttal contention because it fails to take into account the fact that documented fish kills have occurred as a result of draining water from rice fields into catfish farms. 40 CFR 162.11 (a)(6)(ii) provides additional grounds for cancellation for any pesticide

which does not meet or exceed the 162.11(a) risk criteria if the Administrator determines that "when used in accordance with widespread and commonly recognized practice the pesticide generally causes unreasonable adverse effects on the environment." Thus, the Agency is justified in taking action to prevent fish kills from the common practice of draining benomyl-containing water from rice fields into catfish farms.

d. Concentrations Less Than One-Half of the LC50 for Representative Organisms

DuPont [30000/23:1296] contended that a field monitoring study shows that since users do not apply benomyl directly to water, the actual concentration of benomyl in the water of the rice fields is considerably lower than the theoretical concentration calculated by EPA and does not exceed one-half of the LC_{50} for the representative organisms bluegill and Daphnia.

The Agency rejects this rebuttal argument because the regulations state that the risk criteria are exceeded by a maximum calculated concentration based on the highest level of application allowed by the label. The one study cited by duPont, "Monitoring Study: Benomyl applied to flooded rice fields", entailed the application of benomyl at 0.5 lb/acre with two applications at a rate half the maximum allowed by the label. In the duPont studies, the highest concentration of benomyl measured in the water of the rice

fields was 90 ppb. After the water was drained from the rice fields into natural bodies of water, the concentration reached 50 ppb. These concentrations are greater than one-half the LC_{50} for catfish (4 to 6 ppb). This study did not include any fields on which growers applied benomyl at the maximum rates specified on the label, but only fields where growers applied benomyl at the minimum rates on the label. If it is assumed that the application of benomyl at the maximum rate would result in concentrations of benomyl residues twice those actually measured, then the maximum calculated concentration would be greater than one-half the LC_{50} for the bluegill, but not for Daphnia (Leitzke, 1978a).

e. Lack of Movement Downstream

DuPont [30000/23;1296] argued that the field study mentioned above also shows that no significant amount of benomyl moves from the rice fields into bodies of water downstream.

The Agency rejects this argument since in duPont's study samples of water discharged from rice fields showed concentrations of benomyl up to 50 ppb. In duPont's study, samples of water taken 16 to 30 days after the last application of benomyl contained residues in concentrations up to 40 ppb in main drainage ditches and in a canal 1.14 miles from a rice field in Louisiana (Leitzke, 1978a).

2. Rebuttal Relating to the Presumption of Mutagenic Effects

The Agency received comments on the Agency's presumption that benomyl or its metabolite MBC present a mutagenic hazard to man as both a point (gene) mutagen and a non-disjunctive agent. The Agency has evaluated the rebuttals and the additional information submitted concerning these effects and has determined that as of this date the evidence is insufficient to conclude that either benomyl or MBC reacts directly with DNA to cause point mutations or chromosomal aberrations in mammalian systems. However, the evidence cited by the Agency in Position Document 1 and additional material submitted during rebuttal support the presumption that benomyl or its metabolite MBC is a spindle poison capable of inducing non-disjunction. Spindle inhibition could result in aneuploidy or polyploidy; both are chromosomal aberrations of concern.

In the following sections the Agency addresses the arguments submitted in rebuttal. The first two sections present general arguments concerning mutagenicity and the Agency's response to these arguments. Additional sections present studies cited as evidence to support the presumption, rebuttal arguments on the Agency's evaluations of these studies, the Agency's response to these arguments, and additional studies submitted in rebuttal.

a. The Status of Mutagenicity Testing

DuPont [30000/23:1296] questioned whether EPA has the authority to regulate a mutagen and asserted that the status of mutagenicity testing is too uncertain to allow EPA to analyze the risk of a compound classified as a mutagen. In support of this position, duPont contended that the only published draft Guidelines (Federal Register, June 25, 1975) specify that the mutagenicity of a compound shall be tested in live mammals. DuPont also claimed that the Agency, in its assessment of the risk of mutagenicity, has not considered the amount of exposure humans might receive from benomyl.

The Agency does not accept this rebuttal attempt. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) confers authority on the Environmental Protection Agency to regulate pesticides to assure that these substances do not cause unreasonable adverse effects on the environment. FIFRA does not limit the types of adverse effects which are of concern. In exercising its authority, the Agency may take regulatory action on the basis of any available test data or other information which adequately delineates that risk.

The Agency is not bound by a rigid definition of what constitutes adequate test data or what constitutes an adequate risk analysis. There is nothing in FIFRA or in the Agency's regulations which require a quantitative risk assessment.

The regulations do not require that a detailed exposure analysis be made when an RPAR notice is issued on the basis of mutagenicity. Since exposure can occur from dermal and/or respiratory routes through the application of the product in both home and agricultural uses, as well as from residues in food, a connection has been established between the use of the pesticide and the resulting exposure to humans. The risk assessment in this document will consider the levels of exposure for each use in determining the resultant hazard.

b. Agency Perspective on Risk of Heritable Genetic Effects

DuPont [30000/23:1296] argued that studies cited by the Agency in Position Document 1 do not demonstrate mutagenic action. Specifically they contended that spindle inhibition, mitotic delay and metaphase arrest are not chromosomal effects, that the bone marrow micronucleus test does not demonstrate heritable effects and that neither micronucleus formation nor lagging chromosomes or bridges are necessarily evidence of chromosome effects.

The Agency rejects this rebuttal argument. The Agency considers data from somatic and/or germinal test systems in order to assess the potential of heritable changes in the human genome. Several biochemical mechanisms could result in such a heritable change in the genetic material of germ cells. Studies are cited which indicate

that benomyl, or its metabolite MBC, has the capacity to inhibit cell division. Total inhibition of cell division could result in polyploidy, and incomplete inhibition may yield aneuploidy. In humans polyploid conceptuses are lost as spontaneous abortions. Aneuploid conceptuses are also greatly selected against during the fetal period, but some can survive into postnatal life. Within this context the Agency considers a mitotic poison to be a potential mutagen.

c. Chromosomal Effects: [Styles and Garner (1974)]

Styles and Garner reported on tests conducted in rats and in cultures of human, mouse, and hamster cell lines. In these studies, benomyl and MBC caused mitotic delay, a low incidence of chromosomal breakage, and multi-nucleation in mammalian cells in culture. Metaphase arrest and micronuclei formation occurred in bone marrow cells of rats treated with MBC; in addition there was a low frequency of chromosomal breakage and formation of anaphase bridges. Benomyl caused similar abnormal arrangements when injected intraperitoneally but not when given orally (EPA, 1977).

(i) Source and Composition of Test Compound

The rebuttor (duPont [30000/23:1296]) pointed out that the source of the benomyl used in the Styles and Garner study was not duPont and that an analysis of purity was not provided.

The Agency rejects this rebuttal attempt. The authors state that the source of the test material was Plant Protection Ltd., Jealotts Hill Research Station, Bracknell, Berkshire, Great Britain. Although no analysis of purity was given, there is no evidence that the compound tested is different from the benomyl used in the U.S. (Chaisson, 1978a).

(ii) Incorrect Cell Line Tested

DuPont [30000/23:1296] asserted that the chromosomal breaks noted in Chang liver cells were actually seen in Hela cells, and that the results were therefore invalid because tumor cells do not exhibit normal microtubule-membrane-spindle interactions.

The Agency rejects the rebuttor's claim that the results are invalid because the observations were made with Hela cells. First of all, the Agency notes that the report by the American Type Culture Collection (Catalogue of Strains 11, 1975) indicates a high incidence of Hela cell contamination in many cell lines including Chang liver cells. Although identifying enzymatic electrophoretic profiles were not provided to help discount the possibility of such contamination with the cells in this study, the results remain useful in assessing the mitotic interaction potential. Transformed cells, as well as non-transformed cells, contain a mitotic apparatus and are dependent upon

spindle formation and function for cell division. The spindle effects observed in the study indicat that benomyl and/or its metabolite MBC is capable of interfering with the mitotic apparatus of a dividing cell. Thus, the results with Hela cells in this study provide one piece of evidence which indicates that benomyl and/or its metabolite MBC are capable of adversely affecting the spindle mechanism (Chaisson, 1978a).

(iii) Misinterpretation of Study

DuPont ([30000/23:1296]) asserted that "the purpose of the study was to assess cytotoxicity, not mutagenicity."

The Agency rejects this rebuttal attempt. The Agency interprets this study as evidence of the mitotic effects of benomyl and related compounds. The nomenclature applied to the investigation does not diminish the impact of the evidence establishing that benomyl and/or its metabolite interfere with the mitotic apparatus (Chaisson, 1978a).

(iv) Insufficient Data

DuPont [30000/23:1296] claimed that there are no data in the Styles and Garner study to support the claim of chromosomal breakage or anaphase bridges.

The Agency accepts this rebuttal argument. Insufficient data were presented by the authors in order to judge the validity of the claim of chromosome breakage

and anaphase bridges. Although Styles and Garner noted a low incidence of these effects, there was no evidence presented regarding their statistical significance (Chaisson, 1978a).

d. Chromosomal Effects: [DeBrander et al. (1976)]

In Position Document 1, the Agency cited a study by deBrander which demonstrated that benomyl and MBC induced multinucleation in mouse cells (EPA, 1977).

DuPont [30000/23:1296] claimed that the Agency misinterpreted this study because the actual event which occurred was "multimicronucleation", a phenomenon which is very different from "multinucleation".

The Agency rejects the rebuttal contention that this study does not show an adverse effect attributable to benomyl. The Agency agrees that the effect observed by deBrander is more correctly identified as "multimicronucleation", a response induced by anti-tubulins. The deBrander test was designed to test for mitotic spindle inhibition alone rather than both chromosomal damage and non-disjunction, which are measured in the classical micronucleus test. Spindle-effects are considered by the Agency to be mutagenic effects, [refer to part (b) of this section (Chaisson, 1978a)].

e. Chromosomal Effects: [Seiler (1976)]

Seiler found that both benomyl and MBC produced dose-related mutagenic effects in the micronucleus test in mice. In addition, lagging chromosomes, anaphase bridges, unequally distributed chromosomes, and tripolar anaphases appeared in mitotic bone marrow cells of treated animals, whereas none of these effects was noted in control cells. The author concluded that the main action of benomyl was the inhibition of the mitotic spindle, which may predispose the chromosomes to nondisjunctional errors (EPA, 1977).

DuPont [30000/23:1296] asserted that Seiler (1976) reported that micronuclei were produced in mouse bone marrow only when benomyl or MBC was administered orally in gum arabic, a solvent known to produce cytogenetic abnormalities, but not when administered intraperitoneally in DMSO. DuPont submitted a report entitled "Study of the Mutagenic Effects of Gum Arabic" (Stanford, 1972) which does show some adverse effects on metaphase chromosomes when rats are fed 5.0 g/kg and 2.5 g/kg gum arabic.

The Agency rejects this rebuttal contention because there is no evidence that the amount of gum arabic used as a carrier would account for all of the results noted by Seiler. The absence of micronuclear effects after intraperitoneal administration can be explained by the lack of solubility of MBC at pH7, which prevented

efficient uptake of the test compound from the peritoneum. The results and conclusions of the Seiler paper remain relevant and the Agency considers this study evidence of benomyl's potential to cause non-disjunction (Chaisson, 1978a).

f. Chromosomal Effects: [Plants]

In Position Document 1, the Agency cited two studies in which chromosomal aberrations were induced in higher plants as evidence that benomyl and MBC are mutagens.

DuPont attempted to rebut the presumption on the basis that "none of EPA's published or draft Guidelines include any reference to mutagenicity assay using plants."

The Agency rejects this rebuttal attempt. The purpose of the Guidelines is to provide guidance regarding the test requirements necessary to achieve registration of pesticides. As duPont noted, the Guidelines do not limit the tests that can be used either for registration or RPAR purposes. Addendum III to the Proposed Guidelines published August 22, 1978 states that positive results in test systems not included in the battery of tests should not be rejected as evidence of mutagenicity (Chaisson:1978a).

g. Chromosomal Effects [Negative Studies Cited in Rebuttal]

DuPont [_)000/23:1296 cited the following studies as evidence that benomyl or MBC does not cause chromosomal effects. Three of these studies were cited by the Agency in Position Document 1; the other three were submitted by DuPont in rebuttal.

(i) Dassenoy and Meyer, 1973

In the Dassenoy and Meyer study, cited in Position Document 1, the authors found that benomyl gave a negative response with Allium cepa. The Agency accepts this as a valid negative study.

(ii) Sherman et al., 1975

The Sherman et al. (1975) dominant lethal study in rats was cited in the RPAR position document. The Agency accepts this as a valid negative study.

(iii) Hoffman and Peh, 1974

A review of the dominant lethal study by Hoffman and Peh (1974) was contained within the WHO Pesticide Residues Series as cited in the RPAR position document. The Agency does not accept the negative conclusions of this study because the data were not submitted for evaluation. The Agency notes, however, that the results of this study are consistent with those of Sherman.

(iv) Mollet: 1976

Mortality, somatic recombination and induced mutations were measured in Drosophila melanogaster larvae fed at sub-toxic levels (0.5 to 26 mM of MBC in a live yeast suspension). The results showed no significant increase in male mosaic and spot frequency when compared with the corresponding control level. No somatic recombination and mutation were detected. The Agency considers this study valid supporting evidence that direct genetic alteration in higher organisms via recombination is not evident. The Agency notes that this author did not exclude the possibility of an effect on somatic cells of the larvae.

(v) Siebert, Zimmerman, and Lemperle, 1970

Benomyl, as Benlate^{R}, was tested in Strain D4 of Saccharomyces cerevisias for induction of gene conversion at concentrations as high as 1000 ppm. Benomyl showed no activity in this system. The Agency accepts this study as valid and considers it to be supporting evidence that benomyl's mechanism of action is not via direct chromosomal damage. This test system is sensitive for a recombination mechanism in which breaks and genetic transfer to the homologous chromosome occur. The Agency does not accept duPont's interpretation that the results of this study imply that no chromosomal effect (including aneuploidy) can occur. Aneuploidy would be caused by a mitotic interference.

(vi) Seiler, 1977

Thi dominant lethal study in rodents with MBC is cited in the Seiler study. However, no details or data were published or submitted to the Agency for evaluation. The Agency does not accept this citation as evidence of a negative result until an evaluation is possible.

(vii) Conclusions Concerning Negative Studies Cited by duPont

In summary, the negative studies in Drosophila, Saccharomyces, and Allium support the hypothesis that benomyl does not produce direct chromosomal damage. The Agency does not accept these studies as evidence that chromosomal effects such as aneuploidy could not result from other mechanisms such as spindle interference.

The negative dominant lethal studies discussed above support the conclusion that benomyl does not cause direct chromosomal damage. This evidence is not sufficient to dismiss the possibility that genetic effects can be produced in mammalian cells via another mechanism such as mitotic interruption and spindle interference (Chaisson, 1978a).

h. Point Mutations: [Dassenoy and Meyer (1973)]

In Position Document 1, the Agency cited as evidence of point mutation a study by Dassenoy and Meyer in which auxotrophic mutants were isolated at rates significantly greater than the control rate when conidia of Fusarium oxysporum were treated with benomyl (EPA, 1977).

(i) Inappropriate Test System

DuPont:[30000/23:1296] contended that mutagenicity assays for fungicides should not be run in fungi since biocidal compounds should not be evaluated with respect to human safety in the organisms that they are selected to control.

The Agency rejects this rebuttal attempt. The results in Fusarium are not the only factor being considered in the evaluation of human risk. Fungi are useful as test species because of their sensitivity. Although fungi and higher eucaryotic forms display differences in the mitotic process, tests on fungal species give relevant evidence of the mechanism of action of a test compound such as benomyl (Chaisson, 1978a).

(ii) Inadequate Study

The rebuttors (duPont:[30000/23:1296] and Sisler:[30000/23:1716]) contended that point mutational activity was not demonstrated in the Dassenoy and Meyer study. They cited the probability of selection of pre-existing benomyl resistant mutants or non-disjunction events as possible alternative explanations of the effects observed. In addition, duPont [30000/23:1296] cited the genetic instability of Fusarium, the lack of identification of the carrier solvent, and the absence of back mutations as reasons for disqualifying this study.

The Agency accepts the rebuttal argument that poin mutational activity was not demonstrated unequivocally in this study. Although the control rate of 0/100,000 spontaneous revertants suggests a minimal probability of genetic instability, tolerant strain selection is possible. Therefore, the Agency has concluded that the evidence could be interpreted as either selection of background mutants or a non-disjunction event (Chaisson, 1978a).

i. Point Mutations: [Seiler (1972)]

In Position Document 1, the Agency cited a study by Seiler which demonstrated that MBC and other benzimidazoles induce base-substitution mutations as detected by the Ames test without metabolic activation. Salmonella typhimurium strains his G46 and TA1530 were used. In addition, forward mutations were induced in Salmonella strain LT-2 (EPA, 1977).

DuPont [30000/23:1296] cited several omissions in the study such as the failure to explain the protocol completely, the failure to define the number of experiments, replicate dishes or variations, the failure to describe the zone of activity in the spot test, and the failure to show a dose response relationship.

The Agency accepts the rebuttal argument that the Seiler study had certain shortcomings which limit the utility of this study for determining the potential point mutagenic risk attributed to benomyl (Chaisson, 1978a).

j. Point Mutations: [Kappas (1976)]

In Position Document 1, the Agency cited a study by Kappas which demonstrated that benomyl induces base-substitution mutations without metabolic activation in Salmonella typhimurium strain TA 1535. Reverse mutations were induced in Escherichia coli strain WP2 uvrA, which is excision-deficient but not in strain WP2 which is excision proficient. The authors concluded that benomyl may be incorporated into DNA but that the abnormal base is removed in repair-proficient strains but not in repair-deficient strains (EPA, 1977).

DuPont [30000/23] argued that "this result, lacking a dose response relationship, cannot stand alone as evidence for point mutational activity and requires confirmation in a thorough standard plant incorporation assay."

The Agency accepts the rebuttal argument that this study alone is inadequate to determine if benomyl is a point mutagen and that the point mutational activity needs confirmation through additional tests (Chaisson, 1978a).

k. Point Mutations: [Rebuttals Relating to More Than One Study]

(i) Repair Deficient Strain Used

The rebuttor (duPont [30000/23:1296]) objected to the use of results obtained in repair deficient strains because human cells possess repair mechanisms.

The Agency rejects this rebuttal argument. Tests in repair deficient strains are acceptable models for mutagen detection. The absence of repair capacity increases the sensitivity of the test system and maximizes the opportunity to detect induced mutations. Such systems are valuable tools in assessing the intrinsic mutagenic capacity of the compound even though direct quantitative extrapolation to repair competent cells is not possible (Chaisson, 1978a).

(ii) Solvent Properties

DuPont [3000/23:1296] asserted that the positive results obtained when DMSO was used as a solvent must be regarded with suspicion. The unusual solvent properties of DMSO (e.g. enhancement of chemical reactions, alteration of biological molecules, and alteration of cellular permeability) are sufficient grounds for questioning the validity of positive results.

The Agency rejects this rebuttal argument. Although DMSO can affect the in vitro culture conditions or membrane integrity, the use of this dispersal agent does not invalidate the results of the study. DMSO is a generally recognized carrier, and in the absence of data to suggest a biochemical problem which could influence the expression of mutagenic potential, this vehicle is considered an appropriate solvent.

(iii) Lack of Evidence for Incorporation into DNA

DuPont [3000/23:1296] contended that "there is no evidence that benomyl or MBC are incorporated into DNA." They contended that the Seiler papers (1972, 1975) cited by the Agency in Position Document 1 do not present an unequivocal demonstration that benzimidazole is incorporated into DNA.

The Agency accepts this rebuttal contention. The Agency cited the Seiler studies as supporting evidence for the Kappas study. However, the Agency agrees that these results with benzimidazole do not prove that similar activity would be found with benomyl or MBC (Chaisson, 1978a).

1. Point Mutations: [Additional Studies Submitted in Rebuttal]

DuPont has submitted the following studies as evidence that benomyl, MBC, or 5-HBC do not cause point mutations. Some of these studies were also cited by Sisler as evidence of lack of point mutation potential of MBC.

(i) Haskell Laboratories, 1977,1978

Benomyl was tested in Salmonella typhimurium strains TA 1535, TA 100, TA 1537, TA 1538 and TA 98 with and without metabolic activation. The technical grade was tested at doses of 200 to 10,000 ug/plate. Positive results were found in the frame-shift detection

strain with metabolic activation. Benomyl, analytical grade, was retested twice in the same strains at concentrations ranging from 1000 to 15,000 ug/plate. Weakly positive results were shown in TA 1537, a frame-shift tester with metabolic activation. In another retest, benomyl as Benlate^{R}-wettable powder gave negative results at 100 to 750 ug/plate with activation and 100 to 1200 ug/plate without activation. Benomyl, 99 percent pure, was tested in doses from 40 to 500 ug/plate, with only strain TA 1537 without activation showing borderline positive results. The major animal metabolite, 5 HBC, was tested in this system at doses of 200 to 20,000 ug/plate with negative results.

The Agency has validated these studies and has concluded that the positive result obtained with the technical grade benomyl may have been due to a contaminant. Since some trials were run at concentrations far below those which are cytotoxic, these data are not accepted as proof that benomyl cannot induce point mutations (Chaisson, 1978a).

(ii) Shirashu, Mariya, and Kato, 1978

Benomyl was tested in the recombinant assay with B. subtilis strains M45 and H17. No inhibition zones were noted. The Agency accepts this study as valid.

Benomyl at a concentration of 5 to 1000 ug/plate was tested in Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100 and Escherichia coli WP2 with and without metabolic activation. Benomyl induced no increase in mutation in any strain in any test condition. The Agency has evaluated this study and considers the results valid.

Benomyl was administered by gastric intubation of two doses (200 or 1000 mg/kg), and S. typhimurium G 46 was inoculated intraperitoneally to male ICR mice. (Total doses were 400 or 2000 mg/kg). The results of this host-mediated assay were negative. The Agency has evaluated this study and considers the results valid (Chaisson, 1978a).

(iii) Lamb and Lilly (Abstract) 1973

Benomyl, as Benlate^{R}, was fed to male fruit flies (D. melanogaster) at a dosage of approximately 14 ug in a sex-linked recessive lethal test. No evidence of mutagenic potential was presented, and the Agency agrees with the authors that this submission is not adequate to support a conclusion of a negative result since the data base was limited and incomplete (Chaisson, 1978a).

(iv) Conclusion Concerning Additional Studies Submitted by duPont.

In summary, the Agency considers the valid negative mutagenicity studies as supportive evidence that the mechanism of action of benomyl is not via point

mutations. However, these negative studies cannot be construed as conclusive evidence of the inability of benomyl or its metabolites to produce point mutations.

3. Rebuttals Relating to the Presumption of Teratogenicity

In Position Document 1, the Agency cited three studies in which benomyl was subjected to teratogenicity testing. Teratogenic effects were noted when Schtenberg and Torchinski administered benomyl orally to Wistar rats. Torchinski also induced teratogenic effects in Wistar rats by administering benomyl by gavage. However, Sherman et al. did not observe any teratogenic effects when Charles River-CD rats were administered benomyl in their diet. The Agency concluded that the anticipated dermal exposure to benomyl for women of child bearing age is high relative to the dose which produced teratogenic effects in animals; it issued a RPAR for pesticide products containing benomyl which are registered for home use (EPA, 1977).

a. Negative Studies

DuPont [30000/23:1296] attempted to rebut the presumption by citing animal studies which showed evidence that neither benomyl nor MBC is a teratogen.

The Agency rejects this rebuttal attempt. The negative teratogenic potential in Charles River-CD strain of rats does not rebut the positive findings in the

Wistar strain. As stated in Position Document 1, the Agency used the more sensitive strain to determine the teratogenic potential of benomyl. In addition, although duPont submitted a negative teratogenic study for MBC, Delatour et al. have reported positive results (Delatour, 1976).

b. Method of Administration

The rebuttor (duPont:[30000/23:1296]) claimed that the intubation method used by Schentenberg and Torchinski is a questionable method of administration because the metabolic capacity of the animal is overwhelmed and acute effects are expressed.

The Agency rejects this rebuttal argument. Based on accepted scientific principals expressed in the Proposed Guidelines, intubation is an appropriate method of administration and is probably the most common method used in teratology testing (Burnam, 1978a).

c. Validity of Test

The rebuttor (duPont:[30000/23:1296]) questioned the validity of the Schentenberg and Torchinski study claiming the design was inadequate, concurrent controls were lacking, the number of fetuses examined was insuffient, and details concerning the type or number of abnormalities per fetuses were lacking.

The Agency rejects this rebuttal attempt. Although the study was flawed in many of the aspects listed by duPont, serious adverse fetal effects which were not evident at 62.5 mg/kg/ day were noted, in a dose-dependent manner, at 125, 250, and 500 mg/kg/day. The additional work

by Torchinski (1973) provided confirmatory evidence that benomyl has the potential to produce teratogenic or fetotoxic effects. In view of the deficiencies in the Russian studies, the Agency contracted for a teratology study in an attempt to verify the results observed by Shentenberg and Torchinski (Burnam, 1978a).

d. Exposure

The rebuttor (duPont:30000/23:1296) claimed that the assumptions used by the Agency to calculate possible exposure were grossly in error. Experiment-derived exposure data for home garden use was submitted.

The Agency has now reviewed exposure and dermal absorption data and has revised its original estimates. The new estimates of exposure and risk will be discussed in parts C and D of this Section.

4. Rebuttals Relating to the Presumption of Reduction in Spermatogenic Activity

In Position Document 1, the Agency cited studies which identify the testes as a primary target of benomyl. These included acute and subacute oral studies in which benomyl administered by intubation to rats induced testicular damage. Inhalation toxicity studies showed a reduction in spermatogenic activity in rats and dogs (EPA, 1977).

a. New Test Available

The rebuttor (duPont:[30000/23:1296]) has not questioned the validity of the studies on which the presumption was based. However, DuPont contends that a more recent inhalation toxicity study submitted in rebuttal, which showed a higher no-observable-effect level in Charles River rats, should be used to determine the no-observable-effect level.

The Agency rejects the duPont contention that the most recent test data should be used to establish a no-observable-effect level. No evidence was provided which negates the results of the earlier inhalation toxicity study in Charles River rats; therefore, the Agency will use 7.5 mg/kg as the no-observable-effect level (Burnam, 1978b).

b. Exposure

The rebuttor (duPont:30000/23:1296) claims that the assumptions used by the Agency to calculate possible exposure to applicators were grossly in error.

The Agency has now reviewed exposure and dermal absorption data and has revised its original estimates. The new estimates of exposure and risk will be discussed in parts C and D of this Section.

5. Rebuttals Relating to the Presumptions Concerning Reductions of Populations on Nontarget Organisms

In Position Document 1, the Agency cited studies which demonstrated that benomyl and MBC are toxic to earthworms. The Agency concluded that under normal use

benomyl can reasonably be expected to result in significant reductions of local earthworm populations and issued an RPAR against pesticide products containing benomyl which are registered for outdoor use (EPA, 1977).

a. Reduction of Earthworm Populations Parallelism only in Certain Orchard Uses

DuPont [30000/23:1296] contended that reductions in earthworm populations under actual conditions of use have been observed only in certain orchard uses. They also stated that there is no evidence that reduction in earthworm populations occurs when benomyl is used on field or row crops, and that there is no evidence that earthworms are beneficial organisms.

The Agency rejects this rebuttal contention. The levels of benomyl tested in non-orchard sites (Black, 1975 and Tomlin, 1974) were not greatly in excess of normal field use rates. Although there is no data on the effect of benomyl on earthworm populations in field or row crops, studies by Stringer clearly demonstrate that benomyl is toxic to Lumbricus terrestris (Leitzke, 1978a). Furthermore the argument that earthworms are not beneficial is not germane to the issue of population reduction by benomyl.

b. Lack of Evidence of a "Significant" Local Population Reduction

DuPont (30000/23:1296) argued that granted the fact that benomyl is toxic to earthworms, "significant" local, regional, or national population reductions of earthworms will not occur.

The Agency accepts this rebuttal argument that "significant" population reductions in earthworms would not occur from the use of benomyl. The Agency has concluded, in the light of all available information about this effect, that concern is not warranted because (1) the toxic effects are limited to the site of application because benomyl and its metabolites are essentially immobile in soil and do not leach or move significantly from the site of application; (2) the impact of the loss of earthworms will not extend into adjacent areas because earthworm movement during a year is restricted to only a few meters; (3) the population of the earthworms can rebound to normal a few years after the termination of benomyl treatment since benomyl does not completely eliminate the earthworm population; and (4) the sites of application are reasonably limited, in that entire regions or massive areas of the country are not involved in a regimen of benomyl treatment.

B. Information Submitted on Other Adverse Effects

The Agency solicited further information bearing on the likelihood and significance of potential reactions between benomyl or its metabolites and nitrites to form N-nitroso com-

pounds. This information was solicited because two papers by Borzsonyi et al. suggested the possible formation of N-nitroso compounds and induction of lymphosarcomas in Swiss mice (EPA, 1977).

DuPont [30000/23:1296] submitted experimental data on their attempt to synthesize a sample of the N-nitroso derivative of MBC for use as an analytical standard. Studies designed to investigate possible reaction of MBC with nitrite under conditions simulating the mammalian stomach were also submitted.

The Agency notes that based on a level of sensitivity of 7000 ppm, the evidence seems to indicate that nitroso formation did not occur; however, levels below this figure could be present, since the N-nitroso derivative may act as a neutral compound and be insoluble in dilute acid; hence the extraction procedures may not recover the N-nitroso compound if it is formed. Therefore, despite duPont's extensive experimentation, the question of N-nitroso formation remains open and unresolved (Day, 1978).

C. Exposure Analysis

DuPont [30000/23:1296] and the U.S. Department of Agriculture (Walla, 1978) provided data on patterns of benomyl use which the Agency has used both to identify the populations exposed to benomyl and to estimate the extent of the populations' exposure. In addition, duPont submitted new dermal absorption studies [30,000/23:1296].

1. Dietary Exposure

In Position Document 1, the Agency assumed that the average person would consume 0.03 mg/kg of benomyl or its benzimidazole metabolites per day. This amount represents the maximum dietary exposure which would result when residues of benomyl are present in individual foods at tolerance levels and when all foods are assumed to be treated. The Agency now believes that 0.02 mg/kg/day of benomyl or its benzimidazole metabolites is a more realistic estimate of dietary exposure (Johnson, 1979). This figure was derived from consideration of the actual percentage of crops treated with benomyl. MBC may also be present on crops which have been treated with thiophanate-methyl; however, 40 CFR section 180.3 (d)(10) prohibits the benzimidazole moiety to exceed the highest established tolerance for a pesticide having this metabolite.

2. Applicator Exposure

The Agency's major concern focuses on the level of exposure of applicators to benomyl. The estimate of exposure for benomyl application is based on the following four studies. The Agency used the model developed by Jegier (1964) to estimate the exposure of mixer/loaders and the pilot for aerial application. The duPont data submitted in rebuttal [30000/23:1296] were used to estimate exposure from hand spraying during home use. Studies by

Wolfe and Durham (1967) were used to estimate exposure for other uses. The USDA/State/EPA Benomyl Assessment Team report was used to estimate the daily and yearly exposures. The values calculated from these models are summarized in Table II-2 and Appendix I.

The applicators with the greatest potential for exposure to benomyl are the mixer/loaders for aerial application and the applicators using airblast equipment. The total body dose of benomyl each of these applicators would receive was calculated assuming complete uptake for the oral and inhalation exposure and almost no exposure through dermal absorption.

In Position Document 1, because no data on dermal absorption of benomyl were available, the Agency assumed that 10 percent of benomyl that came in contact with the skin would be absorbed. DuPont [30000/23:1296] submitted a study on the effect of time and dose on the absorption of benomyl through rat skin. This study was reviewed by the Agency and was used to estimate the total total body dose of benomyl from dermal exposure (Appendix II).

Table II-2. Use Patterns and Applicator Exposure

USE PATTERN	POPULATION 1/	HRS/DAY 1/	EXPOSURE MG/KG DERMAL/HR 2/	EXPOSURE MG/KG INHALATION/DAY 2/
1. Rice (aerial)				
Pilots	80	3	0.02	0.003
Mixer/Loader	200	6	1.8	0.24
Flaggers	300	6	0.19	0.00024
2. Soybeans (aerial)				
Pilots	200	3	0.02	0.003
Mixer/Loader	500	6	1.8	0.24
Flaggers	700	6	0.19	0.00024
3. Stone Fruits (aerial)				
Pilots	120	3	0.02	0.003
Mixer/Loader	300	6	1.8	0.24
Flaggers	240	6	0.19	0.00024
4. Stone Fruits (airblast)				
Commercial	60	7	0.5	0.005
Private	3000	8	0.05	0.006
5. Grapes (aerial)				
Pilots	20	3	0.02	0.003
Mixer/Loader	40	8	1.8	0.32
Flaggers	50	8	0.19	0.00032
6. Grapes (airblast)				
Commercial	60	3	0.5	0.002
Private	40	4	0.5	0.003
7. Berries (aerial)				
Pilot	15	3	0.02	0.003
Loaders/Flaggres	20	5	1.8	0.2
8. Berries (airblast)				
Commercial	28	3	0.5	0.002
9. Berries (ground)				
Private	210	3	0.05	0.003

Table II-2. Use Patterns and Applicator Exposure (Continued)

USE PATTERN	POPULATION 1/	HRS/DAY 1/	EXPOSURE MG/KG DERMAL/HR 2/	EXPOSURE MG/KG INHALATION/DAY 2/
10. Fruit Crops (aerial)				
Pilots	20	3	0.02	0.003
Mixer/Loader	40	8	1.8	0.32
Flaggers	50	8	0.19	0.00032
11. Fruit Crops (airblast)				
Private	21,000	6	0.5	0.004
12 Citrus (airblast)				
Applicators	714	8	0.5	0.006
13. Homeowner				
Turf	75	0.5	0.04	0.0002
Ornamentals	534,000	0.5	0.04	0.0002
14. Vegetables				
All Types	1515	2	0.04	0.0006

1/ ESTIMATED USDA/STATE/EPA BENOMYL ASSESSMENT TEAM REPORT
2/ SEE APPENDIX I

The greatest amount of dermal exposure would occur during during the mixing and loading of the product for aerial application; however, no more than 0.006 mg/kg body weight would be absorbed during an 8 hour day at this exposure level (refer to Appendix II). A proportion of this maximum value depending on how many hours per day the applicator worked was added to the mixer/loader total body doses; for all other activities the amount absorbed is too low to be mathematically significant and will be discounted. The total body doses calculated for benomyl are contained in Table II-3.

D. Risk Assessment

The RPAR criteria for risk reflect a concern with a pesticide's potential to produce adverse effects on man and the environment. The frequency and severity of the anticipated adverse effects vary with the extent of exposure to the pesticide, and the anticipated exposure is dependent on the pesticide's mode of use.

1. Aquatic Risk

As a result of its use on rice, benomyl poses a significant hazard to natural, local populations of channel catfish and other Ictalurids; it can also cause a decrease in fish-food organisms from chronic exposure to its longer-lived metabolite MBC, thus posing an indirect hazard to other fish as well. As a result of possible drift from multiple aerial

Table II-3. Total Body Dose Calculations

USE	POPULATION [1]	HRS/Day	TOTAL BODY DOSE MG/KG/DAY DERMAL [2]	INHALATION [3]	TOTAL [4]
1. Rice (aerial)					
Pilots	80	3	0	0.003	0.023
M/L	200	6	0.004	0.24	0.264
Fl.	300	6	0	0.00024	0.020
2. Soybeans (aerial)					
Pilots	200	3	0	0.003	0.023
M/L	500	6	0.004	0.24	0.264
Fl.	700	6	0	0.00024	0.020
3. Stone Fruits (aerial)					
Pilots	120	3	0	0.003	0.023
M/L	300	6	0.004	0.24	0.264
Fl.	240	6	0	0.00024	0.020
4. Stone Fruits (air blast)					
Commercial	60	7	0	0.005	0.025
5. Private	3000	8	0	0.006	0.026
6. Grapes (aerial)					
Pilots	20	3	0	0.003	0.023
M/L	40	8	0.006	0.32	0.346
Fl.	50	8	0	0.00032	0.020
7. Grapes (air blast)					
Commercial	60	3	0	0.002	0.022
8. Private	40	4	0	0.003	0.023
9. Berries (aerial)					
Pilots	15	3	0	0.003	0.023
M/L	20	5	0.004	0.2	0.224
10. Berries					
Commercial	28	3	0	0.002	0.022

Table II-3. Total Body Dose Calculations (Continued)

USE	POPULATION 1/	HRS/Day 1/	TOTAL BODY DOSE MG/KG/Day DERMAL 2/	INHALATION 3/	TOTAL 4/
11. Berries (ground)					
Private	210	3	0	0.0003	0.020
12. Fruit Crops (air blast)					
Pilots	20	3	0	0.003	0.023
M/L	40	8	0.006	0.32	0.346
Fl.	50	8	0	0.00032	0.020
13. Fruit Crops (air blast)					
Private	21,000	6	0	0.004	0.024
14. Wheat (E) (aerial)					
Pilots	10	3	0	0.003	0.023
M/L	10	7	0.005	0.28	0.305
Fl.	10	7	0	0.0003	0.020
15. Homeowner	75	0.05	0	0.0002	0.020

1/ ESTIMATED USDA/STATE/EPA BENOMYL ASSESSMENT TEAM REPORT.
2/ SEE APPENDIX I.
3/ ASSUMES 100% OF RESPIRED BENOMYL.
4/ TOTAL REPRESENTS THE SUM OF THE DERMAL AND INHALATION PLUS THE ASSUMED ORAL DOSE (BACKGR RESIDUE OF BENOMYL AT TOLERANCE LEVELS = 0.02 MG/KG/DAY). TOTAL BODY DOSE ASSUMES COMPLETE UPTAKE FOR ORAL AND INHALATION EXPOSURE AND LIMITED DERMAL ABSORPTION AS OUTLINED IN APPENDIX II.

applications on berries and orchards, benomyl also poses a potential threat to sensitive aquatic species (Leitzke, 1978b). On the basis of currently available information, the Agency is unable to quantify this risk; however, actual evidence of fish kills exists only when the product was misused.

2. Human Risk

The risk assessment for benomyl is based on the premise that a pesticide product which has been shown to induce teratogenic, spermatogenic, or mutagenic effects in test species will present a hazard to man[1/] which will vary depending on the extent of exposure.

1/ The Agency has not yet developed a standard procedure for defining mutagenic risk in quantitative terms. At the present time, much attention is being focused on developing a battery of test systems and other data that are predictive of mutagenic risk in humans. Until such time as more quantitative methods and procedures for risk estimation are developed for each mutagenic endpoint of concern, the Agency will evaluate each mutagenic chemical on a case by case basis, taking into account all available test data. The approach taken by the Agency will of necessity be conservative in order to assure that man and the environment are protected from the risk of "unreasonable adverse effects" through the action of mutagenic agents. The evolving nature of methodology in the field of mutagenicity testing dictates that the Agency will revise its risk estimation procedure for future chemicals under evaluation as superior risk predictive models and other relevant information become available. As well, the Agency will revise its risk estimates for chemicals which have previously been subjected to risk assessments if additional more relevant test data and other predictive information are developed.

a. Mutagenicity

(i) Point Mutations

The Agency presumed that benomyl or its metabolite MBC presents a mutagenic hazard to humans by producing point (gene) mutations. The data sources used in the original Position Document for point mutations are summarized in Table II-4. Work by Seiler (1973, 1975) suggests that benzimidazoles can be incorporated into the DNA of E. coli. The similarity of the chemical structures of MBC and benomyl to the purines suggested to Seiler that these compounds may act as base analogues.

Further support for the hypothesis that benomyl and/or MBC can cause point mutations is provided by the demonstration that these compounds induced forward mutations in Fusarium (Dassenoy) as well as by positive test results in several strains of bacteria. However, test results in the microbial systems were conflicting or not completely reproducible and did not show dose response. Specific rebuttals on these tests are discussed in the Rebuttal Analysis section of this document.

Fahrig and Seiler (1979) have also demonstrated coat color changes in mice treated in utero with MBC. Their findings are less than definitive, but are consistent with a point mutation mechanism. The utility of the mouse spot test is still being investigated by experts in the field of mutagenicity.

Table II-4. Studies Cited for Evidence of Point Mutations

Test Model	Compound	Citation
Fusarium oxysporum auxotrophic mutants	benomyl, MBC	Dassenoy and Meyer, 1973
Salmonella typhimurium his G46, TA1530, TA1534, Lt-2 TA1531, TA1532, his D3052 (without ativation)	MBC, benzimidazoles	Seiler, J.P., 1972
E.Coli WP2, WP2 (uvrA), CM61 (uvrAlexA) S. typhimurium TA1534, TA1538	benomyl	Kappas, Green, Bridges et al., 1976
incorporation studies with E. Coli	benzimidazoles	Seiler, J.P., 1972
incorporation studies with E. Coli	benzimidazoles	Seiler, J.P., 1973
S. typhimurium spot test, host mediated his G46 and TA1530, TA1950 (no mutations for benomyl doubtful for MBC)	benomyl, MBC	Ficsor, G. and Bordas, 1978
*Mouse cytogenetic spot test	MBC	Fahrig, R. and Seilerr, J. P. unpublished

*Not cited in Position Document 1.

The available information on the point mutagenesis of benomyl and MBC does not clearly demonstrate a risk of point mutations to humans, and hence the presumption that benomyl and/or its metabolites meet or exceed the criteria for point mutation has been successfully rebutted. However, various studies suggest that benomyl may cause point mutagenesis and the Agency is not assured of the safety of benomyl with regard to this mechanism, particularly in light of the fact that test data are available from only a selected number of the available test systems designed to detect point mutational events. Due to the limited data base and the equivocal results achieved in the test systems which were studied, the Agency will be requesting that additional studies be performed to assess the point mutagenic potential of benomyl and metabolites should registration be continued.

(ii) Chromosome Breakage

The Agency's presumption of mutagenic risk from chromosomal effects was summarized in the PD 1 on benomyl. Reports of chromosome-breaking activity were cited in references on higher plants (Zutshi and Kaul, 1975) and on mammalian cells in culture and *in vivo* (Styles and Garner, 1974). Other studies were unable to confirm these observations. Thus the status of the ability of benomyl or its metabolites to break eukaryotic chromosomes has not been adequately resolved.

(iii) Spindle Inhibition

The other chromosomal mutational effect which has been observed with benomyl or its metabolite MBC deals with the inhibition of the nuclear division spindle. There is substantial evidence that benomyl and/or its metabolite MBC are spindle inhibitors capable of inducing the failure of chromosomes to separate properly at anaphase. This type of effect may lead to numerical chromosomal mutations such as aneuploidy, which occurs when one or a few chromosomes are gained or lost during cell division, or polyploidy, which occurs when the whole spindle is inhibited and there is a failure of nuclear division. Both aneuploidy and polyploidy have been produced in plant and animal cells by physical and chemical agents which block the spindle (Brachet, 1957; Burnham, 1962).

The consistency of effects observed in a variety of test systems, namely in vivo mammalian studies (Styles and Garner, 1974; Seiler, 1976), mammalian cells in culture (Styles and Garner,1974; deBrander et al., 1976), biochemical studies on fungi (Hammerschlag and Sisler, 1973; Richmond and Phillips, 1975, Kappas et al., 1974; Davidse, 1973; Bignami et al. 1977), rat tubulin in vitro (Seiler, 1977; deBrander et al., 1976), and plant cytological and genetic studies (Zutshi and Kaul, 1975; Boyle, 1973) support the mechanism of spindle inhibition for benomyl and/or MBC.

Recent studies (Wilson et al., 1974; Davidse and Flack, 1977) have provided information concerning the process of inhibition of the nuclear division spindle fibers at the molecular level. The nuclear division spindle fibers are composed of microtubules, which are protein fibers within cells that are essential for many structural and functional activities. Microtubules consist of polymerized protein subunits called tubulin. Various drugs which block cells in metaphase appear to act by binding to tubulin monomers and preventing their polymerization into microtubules. MBC, colchicine, and several other chemicals appear to bind at the same specific site on tubulin.

(a) Animal Studies (in vivo)

Styles and Garner (1974) demonstrated that benomyl and MBC (1000 mg/kg, intraperitoneally) and MBC (1000 mg/kg, perorally) produced metaphase arrest in rat bone marrow cells. As well, in studies designed to measure micronucleus production and blood levels following peroral administration of two daily doses of 50, 100, 500 and 1000 mg/kg MBC to mice, Seiler (1976) found that 100, 500, and 1000 mg/kg doses of MBC produced dose-dependent increases in the number of cells containing micronuclei. At a dose level of 50 mg/kg, the fraction of cells containing micronuclei remained at background level. The blood values of MBC following 100 and 500 mg/kg peroral administration reached peak values of 12 and 22 ug/ml, respectively. The administration of 100 and 500 mg/kg doses of MBC intraperi-

toneally did not result in increased micronucleus production and gave similar blood levels of MBC (8ug/ml).

Seiler (1976) made other observations to elucidate the mechanism of micronucleus formation in MBC-treated animals. Many micronuclei in erythrocyte precursors were rather large, suggesting the presence of whole rather than broken chromosomes. Seiler noted that other investigators had observed similar phenomena with anti-mitotics such as colchicine and vinblastine.

Also, configurations suggesting spindle inhibition were noted in nucleated bone marrow cells from rats treated orally with MBC; these included increased metaphase frequency, lagging chromosomal material, unequal distribution of chromatin during division, and multipolar mitoses.

Lastly, Seiler treated Chinese hamsters with MBC (two daily doses of 1000 mg/kg administered orally) and analyzed bone marrow cells arrested in metaphase for chromosome aberrations; no evidence of chromosome breakage was found.

(b) Animal studies (in vitro)

Culture metaphase arrest was found in Chang liver cells exposed to 2 ug/ml MBC, but not in cells exposed to 0.02 mg/ml (Styles and Gardner, 1974). In addition benomyl and MBC produced micronucleation in the MO mouse cell line used by DeBrabander at 10 ug/ml but not at 1 ug/ml.

(c) Polymerization Studies (in vitro)

In vitro studies on the inhibition of tubulin polymerization support the hypothesis that benomyl and/or MBC function as a spindle poison. Seiler (1977) demonstrated that polymerization of rat neurotubulin was not inhibited by about 2 ug/ml MBC,[2/] but 25 and 100 percent inhibition occurred at about 10 and 20 ug/ml respectively. Consistent with these observations, Davidse (cited by Seiler, 1977) did not observe any inhibition of mammalian tubulin polymerization at about 2 ug/ml. Likewise, DeBrander et al. (1976) found that polymerization of rat neurotubulin was inhibited about 20 percent by 5 ug/ml MBC.

(d) Plant Studies

Numerous cytological studies show that benomyl or its metabolites inhibit the nuclear spindle in fungal cells, and a similar interpretation has been given to the sectoring phenomenon produced in heterozygous fungal clones by these chemicals. Cytological studies in higher plants have produced less substantive information, but certain observations are consistent with the spindle inhibition; these observations include increased mitotic

2/ Molar concentrations in the papers have been roughly converted to ug/ml using the following approximation 5×10^{-5} M MBC = 10 ug/ml.

index, shortening of metaphase chromosomes, some dispersion of metaphase chromosomes instead of organization into a spindle, and lagging chromosomal material during anaphase. Also, c-mitoses (colchicine-like metaphase arrest) have been observed in higher plant cells after Benlate(R) administration; this action is similar to the observations in mammalian cells. Davidse and Flack (1977) demonstrated that polymerization of fungal tubulin could be inhibited by MBC and that it was more susceptible to inhibition of polymerization by MBC than was mammalian tubulin.

(e) Hazard Assessment

We have strong evidence in many test systems across several phyla (both kingdoms) pointing to the ability of benomyl or its metabolites to interfere with the cell division spindle. Furthermore, there are two lines of evidence which indicate that these chemical metabolites may reach the mammalian gonad. The first demonstrates that MBC, and benomyl to a lesser degree, may damage testicular structure in rats (Styles and Garner, 1974). Further evidence is provided by studies by Gardiner (1974), who demonstrated that radioactive benomyl reaches the testes of rats and dogs. Thus, there is an adequate basis for a qualitative presumption against benomyl for initiating potentially heritable spindle effects.

Lacking at this point is definitive evidence that benomyl induces these effects in germ cells. However, some preliminary results from a promising new test system indicate that MBC may produce effects which may lead to chromosomal nondisjunction in germ cells (Tates, 1978). On the basis of all the above information humans exposed to high levels of benomyl may be at risk from the induction of spindle effects. At the present time the Agency does not have the means to estimate the degree of risk from such exposures. However, the existing data are not adequate to demonstrate the existence of a significant risk from these effects at current exposure levels. At such time that the Agency does have the means it may elect to reevaluate this assessment.

b. Teratogenicity

The teratology presumption was based on a study by Schentenberg and Torchinski in which benomyl was embryocidal and teratogenic at doses of 125 mg/kg/day and greater but not at 62.5 mg/kg/day in Wistar rats. The Agency concluded that the Schentenberg study should be confirmed under more controlled circumstances and sponsored a study to replicate the protocol of the Schentenberg study. The results from the EPA sponsored study showed that benomyl was teratogenic at 62.5 mg/kg/day, the lowest dose tested. Therefore, the Agency does not have a no-observable-effect-

level (NOEL) with which to conduct a teratology risk assessment. Both EPA and duPont are conducting studies designed to establish a NOEL and to examine the relationship between methods of administration in producing teratogenic effects. These studies are scheduled for completion by November 1979; at that time the Agency will reevaluate the teratogenic risk of benomyl to humans. Until the Agency obtains the information from these studies, the assumption will be made that the NOEL for teratogenic effects would not be less than the NOEL for spermatogenic effects, the most sensitive effect level for benomyl, and will use 7.5 mg/kg/day to calculate a preliminary margin of safety for teratogenicity. These margins of safety range from 21 for mixer/loaders to 380 the background level from dietary exposure. The teratogenic risk of benomyl will be reevaluated if necessary between the proposed decision and the final decision if the studies indicate significant changes in the NOEL.

c. Spermatogenic Effects

The Agency has no epidemiologic evidence indicating that exposure to benomyl might result in depressed sperm counts. Therefore, the Agency has utilized 7.5 mg/kg, the NOEL observed in rats, which are the most sensitive species tested, to determine the margin of safety for spermatogenic effects. The calculated margins of safety range from 21 for mixer/loaders to 380 the background level from dietary exposure.

III. Benefit Analysis

A. Introduction

This section of the position document was derived from An Analysis of Current Benomyl Uses; Their Benefit, the Role of Alternatives, and Importance to Agriculture from Changes in Benomyl Use Patterns, Part II, which was prepared by the USDA/State/EPA Benomyl Assessment Team. After completing the risk analysis, the Agency determined that it was possible to reduce the risk to humans could be reduced to an acceptable level by methods short of cancellation. The human risk analyses indicated that the use of benomyl does not pose significant risks to the general population through dietary exposure, and applicators are at risk only as the result of inhalation during mixing and loading operation.

The Agency determined that the additional restrictions necessary to reduce risk would cause inconsequential changes in the use patterns or benefits. A quantitative economic analysis was not performed because it was assumed that the use of the chemical demonstrated its benefits. A general discussion of benomyl uses compriseded in this section. A more detailed discussion of the uses listed in Table III-1 is presented in the Assessment team report.

The Agency determined that the hazard to aquatic organisms could not be reduced to an acceptable level short

Table III-1. Benomyl Fungicide Use in the United States - 1977[1/]

Crop	Total Lbs A.I. Used
Soybeans	761,000
Stone Fruits	344,000
Rice	299,250
Citrus	259,694
Bananas	200,000
Grapes	173,692
Peanuts	158,500
Vegetables	151,500
Turf	150,000
Ornamentals	125,000
Pecans	100,000
Apples	96,184
Berries (Strawberries, Blueberries, Raspberries)	71,911
Almonds	63,800
Sugarcane	26,000
Sugar Beets	13,500
Wheat[2/]	11,150
Mushrooms	11,034
Pears	10,928
Elm	7,010
Mangoes	6,000
Avocados	1,628
Pineapples	1,506
Macadamia Nuts	100

1/ Total use based on actual surveys conducted by the Benomyl Assessment Team.

2/ Benomyl use data based on 1976 season due to the extreme drought in 1977.

Table III-2. Rice Acreage by State and Total U.S. (1975, 1976, 1977, and 1978)

State	1975	1976	1977	1978
	Acres Harvested (1,000 acres)			
Arkansas	898	847	837	1,170
California	525	399	308	499
Louisiana	658	568	475	587
Mississippi	171	144	111	215
Missouri	18	14	17	30
Texas	548	508	501	558
Total U.S.	2,818	2,480	2,249	3,059

of cancellation. Thus a complete economic analysis was conducted in order that the Agency might make a decision on the "unreasonable adverse effect" of this use.

B. Rice

1. Use Analysis

There has been considerable variation in the acreage of rice harvested in the United States in recent years (Table III-2). Rice is planted mainly in the southern states of Arkansas, Mississippi, Texas, and Louisiana with small acreages found in Missouri. Significant rice acreage is also planted in California. Benomyl is used on rice in the Grand Prairie of Arkansas, northeast Arkansas, the Mississippi River Delta (including Missouri), southwest Louisiana, and the Gulf Coast of Texas. The other major rice producing areas, the Sacramento and San Joaquin Valleys of California, do not use benomyl. About 19 percent of the U.S. rice acreage planted in 1977, or approximately 422,000 acres, were treated with benomyl.

Benomyl is registered and used to control rice blast and stem rot for all states except California. In addition, a special local needs label which permits the use of benomyl to control sheath rot, brown leaf spot, sheath blight, and leaf smut in Texas was granted. There are no other chemicals registered for control of these rice diseases.

In 1975, benomyl was first registered for foliar application on rice to control rice blast, which is one of the most serious diseases of rice in the United States. Benomyl also controls stem rot, the other major fungal disease of rice. These two diseases cause an estimated 12 to 15 percent loss in rice production annually (Walla, 1978).

Cultural practices are not effective in reducing or controlling stem rot or rice blast . Although the severity of rice blast can be reduced by early planting, the large acreage of many rice farms would not enable the farmers to plant all of the acres early enough in the season. The occurrence of frequent showers during the planting season is also a serious constraint on early planting. Crop rotation was used to reduce the severity of stem rot in the past, but given the existing demand for rice, crop rotation is no longer economically sound. In addition, the pressure of urbanization has reduced land available for rice production, further affecting the feasibility of crop rotation. At present there are no rice varieties that are resistant to the prevalent strains of blast and stem rot. In some cases, using less nitrogen fertilizer will reduce the effect of these diseases; however, the yields will also be drastically reduced. Nor is water management is not effective in controlling rice blast.

2. Economic Analysis

The economic analysis of the use of benomyl on rice was based on the following assumptions:

a. The price of rice was assumed to be $7.00 per hundredweight, the mid-point of the $6.50 to $7.50 per hundredweight price range forecast by USDA for the 1978 season. This price is low relative to prices that have ranged from $8.35 to $13.80 per hundredweight from 1973 to 1977 and does not include an allowance of deficiency payments for prices below $8.53 per hundredweight on national allotment acres. In 1978 deficiency payments were made for 58 percent of the 3.1 million harvested acres.

b. There will be an increase in yield of 500 pounds per acre on the acres which have been treated with benomyl.

c. Benomyl was used to treat the same percentage of the rice crop in 1978 as was treated in 1977.

d. Rice yields, as shown in crop production budgets, were assumed to be produced in the absence of diseases and therefore to be representative of the benomyl treated acreage.

e. The price of benomyl is $16.32 per pound active ingredient (a.i.) ($8.16 per pound of Benlate^{R} 50 WP) as indicated in the Texas Gulf Coast rice production budgets.

f. The first application of benomyl by custom aerial applicators will cost $2.00 per acre. For the second

application, a per acre charge of $1.50 was used because about 25 percent of the time the second application includes an insecticide.

g. Improved grain quality (reduction of "peck") will result in a milling premium of 30 cents per hundredweight to rice growers who use benomyl in Texas and southwest Louisiana.

h. Yield increases of 500 pounds would be attained at the seasonal application rates of either 0.5 or 1.0 pounds (a.i.) per acre. Application rates, to achieve disease control, vary directly with the degree of infestation.

It is estimated that using benomyl throughout the five-state area would increase average rice yields 500 pounds per impacted acre for a total increased value of approximately $17.8 million (Table III-3). Furthermore, benomyl reduces "peck", a discoloration of the rice kernel; this reduction results in an increase of the milling quality of Southwest Louisiana and Texas Gulf Coast rice by approximately 30 cents per hundred weight or $5.0 million. After the cost of benomyl treatments ($6.0 million for material and $1.8 million for application) are deducted, an annual net economic benefit of about $15 million is realized.

Texas is estimated to accrue about $10.2 million, or 68 percent, of the total economic benefits of benomyl use on rice. Increases in net returns per impacted acre in

Table III-3. Treatment Costs and Value of Production Changes for Benomyl Use on Rice by State, 1978

State	Treatment Costs a/			Production Changes b/			Economic Impact c/
	Material Cost	Application Cost	Total Cost	Value of Yield Increase	Value of Quality Increase	Total Value of Production Changes	
	million dollars						
Arkansas	1.97	0.45	2.42	4.50	--	4.50	2.08
Louisiana	1.42	0.33	1.75	3.29	1.04	4.33	2.58
Mississippi	0.10	0.02	0.13	0.22	--	0.22	0.09
Missouri	0.01	d/	0.01	0.02	--	0.02	0.01
Texas	2.53	0.98	3.51	9.76	3.93	13.69	10.18
Total	6.03	1.78	7.82	17.79	4.97	22.76	14.94

a/ USDA/EPA. 1979. Economic Analysis of Benomyl and Thiophanate-methyl. Appendix Table 2.
b/ Ibid. Appendix Table 3.
c/ Total value of production changes minus total treatment costs.
d/ Less than $5,000.

different states varied from $23 to $38. These increases are significant to impacted ice producers, who typically have high production costs and low profit margins (Table III-4).

The economic impact of a benomyl cancellation on rice would be insignificant in terms of the total value of U.S. rice production and the total U.S. economy; therefore it should have little, if any, impact on prices, consumption and U.S. rice exports. However, the economic impact would be significant to the rice producers of Texas, Louisana and Arkansas.

C. Other Uses

Benomyl is a broad spectrum fungicide which controls a wide range of diseases at a low rate of application (2 to 16 ounces of active ingredient per acre). Benomyl was the first major systemic fungicide developed. In addition to preventing fungal disease, benomyl can control fungal infections that are already established; this allows more flexibility in the timing of applications. Also, the systemic activity prevents excessive loss of the fungicide during heavy rainfall. Since benomyl is applied at 14 to 21 day intervals rather than 7 to 14 day intervals, as are alternative fungicides, growers can apply the compound less frequently. This should decrease both labor and application costs.

Table III-4. Per Acre Returns over Direct Production Costs on Rice Acreage Treated with Benomyl and Untreated, by Regions, 1978 a/

Region	Benomyl Treatment Per Season 0.50 lb. a.i. per acre b/	1.0 lb. a.i. per acre c/	Untreated d/
	---------dollars ----------		
Northeast Arkansas	25.86	17.70	2.52
Grand Prairie Arkansas	18.84	10.68	-4.50
Mississippi Delta	-16.53	-24.69	-39.87
Southwest Louisiana	30.18	22.02	-4.29
Texas Gulf Coast			
Upper Counties	-6.75	-14.91	-43.74
Lower Counties	-19.79	-27.95	-57.62

a/ Does not include general farm overhead, land, management costs or government deficiency payments.
b/ USDA/EPA. 1979. Economic Analysis of Benomyl and Thiophanate-methyl. Appendix Table 4.
c/ Ibid. Appendix Table 5.
d/ Ibid. Appendix Table 6.

1. Soybeans

Benomyl is used in the Southeast plus the Louisiana and Texas soybean-producing areas. Warm temperatures and high humidity prevail in these areas and are conducive to the development of plant pathogens that cause serious disease losses. Yield data obtained with the use of benomyl show an average increase of 5.5 bushels per acre. The quality of the soybean also improves when benomyl is applied (USDA[30000/23:1795]).

2. Fruit

The use of benomyl has resulted in a substantial improvement in the level of disease control on several fruit crops. The dramatic reduction in brown rot of stone fruits and the significant reduction in losses due to scab and powdery mildew on grapes and to Botrytis fruit rot of strawberries are particularly important. Benomyl is more efficient against a larger group of pathogens which attack fruit crops than any other fungicide. Although captan and mancozeb have been widely used since the early 1950's, they lack the high anti-sporulation action which benomyl displays against many fungi. Therefore, the loss of benomyl for use in orchards could soon result in increased inoculum levels of several pathogens and could require an increase in fungicide usage. The development of benomyl resistant strains of pathogens is of major concern to orchard growers

Consequently, California stone fruit growers use benomyl only in combination with other ungicides. Pacific Northwest apple and pear growers use benomyl only for post-harvest disease control to reduce the possibility of developing tolerant strains (USDA [30000/23:795]).

3. Sugar Beets

Benomyl is used extensively on sugar beets in the irrigated areas where Cercospora leaf spot is a problem. Although benomyl is labeled only for control of Cercospora sp., it also controls the secondary diseases powdery mildew and Rhizoctonia root rot. Alternate materials registered for use on sugar beets do not control these secondary diseases. In addition, these alternative pesticides are not cleared for beet residues fed to livestock, whereas benomyl is (USDA [30000/23:1795]).

4. Citrus

Citrus producers in Florida are dependent on benomyl for the control of greasy spot and scab. If not controlled, greasy spot can cause serious premature defoliation, tree deterioration, and yield reduction. Scab is a fungal disease of economic importance on several citrus varieties grown for fresh market. Scab also presents a problem in citrus nurseries since certain root-stocks are susceptible to scab (USDA:[30000/23:1795]).

5. Peanuts

One of the most destructi diseases of peanuts is Cercospora leaf spot. This foliage disease occurs wherever peanuts are planted and must be controlled for peanuts to be grown economically in the U.S. Many fungicides are available that provide a certain degree of control of Cercospora leaf spot fungi. In 1973 an estimated 49 percent of all peanuts produced in the U.S. were treated with benomyl. When strains of Cercospora resistant to benomyl were found in 1973, the amount of benomyl used in Georgia, Florida, and Alabama declined drastically. In 1977 benomyl was used on an estimated 22 percent of the peanut acreage. Since the Cercospora fungus has developed resistance to benomyl, a combination of benomyl and either Manzate or Dithane is recommended (USDA [30000/23:1795]).

6. Vegetables

Benomyl is used on the vegetables listed in Table III-5. The percentage of the crop treated ranges from 100 percent for cabbage seeds to 18.4 percent for tomatoes (USDA [30000/23: 1795]).

7. Home Garden Use

Benomyl is used by homeowners for control of tar spot, anthracnose, powdery mildew, leaf spot, apple

scab, and flower blight on shade trees and for control of powdery mildew and black spot on roses. Over three hundred letters, representing thirty-eight states and written by individuals and various associations, were submitted in rebuttal which described their previous use of products containing benomyl and its effectiveness. Alternatives are generally less effective, and more expensive than benomyl resulting from the fact that the alternatives are nonsystematic and thus more treatments may be required for the same result.

TABLE III-5. USE PATTERN OF BENOMYL ON VEGETABLES[1/]

APPLICATION SITE	TOTAL POUNDS AI USED IN 1977	ACRES TREATED	% OF TOTAL CROP
CUCUMBER	8,700	81,235	43.9
CANTALOUPES	9,700	65,362	79.5
WATERMELONS	21,000	171,620	66.7
SQUASH	5,100	22,683	90.0
TOMATOES	42,000	90,694	18.4
CELERY	15,000	30,280	87.5
SNAP BEANS	13,300	139,064	37.3
DRY BEANS	34,200	386,920	24.2
CABBAGE SEED	1,500	2,240	100.0

1/ USDA/STATE/EPA BENOMYL ASSESSMENT REPORT

IV. Risk/Benefit Analysis of Alternative Courses of Action

This section of the Position Document discusses the basis for the Agency's development of regulatory options, evaluates methods of risk reduction, and identifies the options selected for consideration.

A. Basis for the Development of Options

FIFRA provides that the Administrator may cancel the registration of a pesticide whenever he determines that it no longer satisfies the statutory standard for registration which requires (among other things) that the pesticide performs its intended function without "unreasonable adverse effects on the environment" [FIFRA Section 3(c)(5); 7 USC Section 136a(c)(5)]. "Unreasonable adverse effects on the environment" means "any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide" [FIFRA Section 2(bb); 7 USC Section 136(bb)]. In taking any final action under section 6(b), the Administrator is required by statute to "consider restricting a pesticide's use or uses as an alternative to cancellation and shall include among those factors to be taken into account the impact of such final action on production and prices of agricultural commodities, retail food prices, and otherwise on the agricultural economy..." [Section 6(b)].

In effect, FIFRA requires the Administrator to weigh the risks and benefits associated with each use of a pesticide. If he determines for any particular use that the risks exceed the benefits, he must then determine whether those risks can be sufficiently reduced (so that they are outweighed by the benefits) by the imposition of restrictionss upon use through modifications to the terms and conditions of registration (reflected by changes in the labeling) and/or by the classification of the use for restricted use. If he determines that adequate risk reduction cannot be achieved by such regulatory measures, the registration of the pesticide for that use must be fully cancelled.

Under the Rebuttal Presumption Against Registration Process detailed in 40 CFR 162.11, the registrant or applicant may rebut a presumption that a pesticide meets or exceeds the risk criteria by sustaining the burden of proving (1) that "when considered with ... proposed restrictions on and directions for use and widespread and commonly recognized practices of use, the anticipated exposure to an applicator or user and to local, regional or national populations of nontarget organisms is not likely to result in any significant acute adverse effects"; or (2) that "when considered with proposed restrictions on use and widespread and commonly recognized practices of use, the pesticide will not concentrate, persist,

or accrue to levels in man or the environment likely to result in any significant chronic adverse effects"; or (3) "that the determination by the Agency that the pesticide meets or exceeds any of the criteria for risk was in error." In effect, the presumption can be rebutted by showing that the risks are far lower than indicated by the Agency's initial determination; that there is not sufficient exposure to warrant the Agency's concern about the potential risk of the pesticide; or that modifications to the terms and conditions of registration will reduce any potential risk below the level of concern. Where modifications to the terms and conditions of registration which will adequately reduce risks can be achieved without significant impacts on the benefits of the affected use, it is not necessary to undertake a detailed analysis or quantification of benefits. Rather, the in-depth consideration of benefits comes into play only when the risks cannot be reduced by such modifications to the terms and conditions of registration, or where such reduction in risk can only be achieved at a cost which has a substantial impact on benefits.

Concerning benomyl - except as it is used on rice - the Agency has determined that proposed modifications to the terms and conditins of registration will adequately reduce risks, and that such risk reduction can be achieved with only an insignificant impact on the benefits. Concerning

the use of benomyl on rice, the Agency has determined that risk can not be adequately reduced by any method short of cancellation. A detailed analysis, or quantification of the benefits of the use of benomyl on rice was therefore necessary in order to make determination of unreasonable adverse risk, and that analysis is discussed at some length in Section III.

B. Possible Alternate Courses of Action

Evaluation of the risk and benefit data suggests these principal regulatory options:

1. Continue registration of the use;
2. Continue registration of the use; amend the terms and conditions of registration;
3. Cancel the use.

1. Option 1: Continue Registration of the Use

Option 1 would indicate that the Agency concludes that the benefits associated with each use of benomyl outweigh the respective risks, and that therefore, the use in question will not cause unreasonable adverse effects. This option would not reduce the risk of adverse reproductive effects to applicators during the mixing/loading and flagging operations for aerial application or during the airblast operation. Under this option the risks associated with mutagenic, spermatogenic, and teratogenic effects would remain at the present level. Likewise, the risk associated with the

use of benomyl on rice would remain at the same level. Field tests show that residues of benomyl in water drained from rice fields which were treated at minimum label rates are greater than the LC_{50} for channel catfish. If maximum label rates are applied, residues of benomyl greater than one-half the LC_{50} for bluegill can be expected as well. This option would not result in any adverse economic impacts and would retain the usefulness of benomyl as an economical, effective tool for the control for fungi. The choice of this option would indicate that the Agency is willing to tolerate the highest risk in return for the highest possible benefits.

2. Option 2: Continue the Registration of Benomyl for All Uses and Amend the Terms and Conditions of Registration

The adoption of option 2 would indicate that the Agency concludes that the benefits of benomyl's continued use will outweigh the risks after certain terms and conditions of registration are amended. The terms and conditions which have been considered in conjunction with this option are enumerated below.

a. Discussion of Proposal to Require Reduction of Application Rates for Rice

This option is designed to reduce the residues of benomyl to which aquatic organisms are exposed when water is drained from rice fields after application of benomyl by amending the label rate to include an application rate of 1/4 pound active ingredient per acre. Benomyl is registered to control rice blast and stem rot in all states except California when applied twice at 1/2 to 1 pound

active ingredient per acre. A special local needs registration was granted by Texas which permits the use of benomyl at 1/4 to 1/2 pound active ingredient twice a year. The application of benomyl at the lower rate should reduce the levels of benomyl which aquatic organisms are exposed to by a factor of two. This reduction would result if the concentration of benomyl in water is in a linear relationship to the application rate. However, application at this lower rate can result in concentrations greater than the LC_{50} for most of the tested lifestages of the channel catfish. No information currently available indicates whether this option would actually reduce the risk to aquatic organisms.

b. Discussion of Proposed Requirement for Additional Studies

(i) Additional Monitoring Study for Rice Use

This option is designed to provide additional data with which the Agency can more adequately evaluate the risk to aquatic organisms. The Agency has no data on the equilibrium between the adsorption of benomyl to the soil and the water concentration in rice fields. The Agency assumed a linear relation between application rates and water concentration in determining risk. To perform a more precise risk determination, the Agency would require a field monitoring study which involves: (1) replicated fields treated twice at 1/4, 1/2 and 1 pound active ingredient per acre; and (2) residue sampling before and after both application and drainage in the rice fields, the main drainage

ditches, and the nearest body of water at the point of entry and several places downstream . Thus, although this option would not reduce the hazard to aquatic organisms, it would provide information the Agency requires to make a determination of risk to aquatic organisms.

(ii) Additional Gene Mutation Studies

This option is designed to provide additional data with which the Agency can more adequately evaluate the risk of point mutagenic potential for man. The evidence the Agency has available from the point mutation studies on benomyl is inadequate to determine the point mutagenic potential for man. The registrants of benomyl and applicants for registration of pesticide products containing benomyl will be required to submit additional tests to detect gene mutations in the following test systems (1) Drosophila, (2) mammalian somatic cells in culture, and (3) an appropriate eukaryotic microorganism for benomyl and its metabolite MBC.

c. Discussion of Proposed Restrictions to Reduce Applicator Exposure.

(i) Require the Use of Protective Clothing

The population with one of the greatest potential exposures to benomyl consists of persons who are directly involved in the airblast application of benomyl and persons who are involved in the mixing, loading, and transfer

operations for aerial applications. Data from Table II-2 show the theoretical exposure range for these persons when the Agency made the assumption that no protective clothing was worn. The Agency assumed that 85 percent of the body is normally clothed and that the hands, forearms, neck, face, upper chest, and head are not covered. Data from Table II-3 show that the total body dose results from the oral background and inhalation exposure with only an insignificant amount from dermal exposure. Since these exposures could result in a margin of safety as low as 20 for reduction in spermatogenic activity and teratogenic effects (Table II-5), the Agency believes that it is both necessary and prudent to explore means for reducing respiratory contact with benomyl.

Respiratory protection could be attained by requiring that a cloth mask be worn during mixing and loading. Wearing a mask would reduce inhalation exposure to zero. The margin of safety would then be 380, the margin from background due to residues on food. The economic impact of this regulation would be slight.

(ii) Require Water-Soluble Packaging for Packages 5 Pounds and Larger

The projected levels of exposure are greatly influenced by the degree of care exercised in mixing the pesticide solution. In this method of packaging, water-soluble bags containing benomyl would be added to the water, and the

formulation would be released and mixed when the bag dissolved. There would be no dust generated from pouring the products. The adoption of this option would essentially eliminate exposure from mixing/loading operations (Day, 1979).

Adopting this option would not cause any severe economic impact on the use or users of benomyl. The primary economic impacts of this option would be the cost of water-soluble packaging for containers of five of more pounds of formulated wettable powder. Exposure rates to individuals mixing amounts less than five pounds of formulated product for a given application are consdered low enough not to justify water-soluble packaging. The requirement of water soluble packaging is not completely beyond the producer's current technology or marketing techniques. DuPont is currently test marketing formulated benomyl in water-soluble packages as a measuring/mixing convenience.

The estimated additional cost of benomyl to the user, as related to the cost of water-soluble packaging for five or more pounds of formulated product, ranges from $.80 to 1.00 per pound active ingredient. The cost per acre would be about $.60 for approximately 4.5 million acres treated each year with benomyl. This amounts to $2.4 to $3.0 million, based on annual benomyl usage of approximately 3.0 million pounds active ingredient and would not effect the benefits of benomyl usage.

This option is useful because it is a passive protective measure. Applicators would not need to take any stringent protective measures than they do at present. Also, there would be no need for additional enforcement activities in order to monitor compliance with this requirement.

(iii) Require that Certain Uses Be Classified for Restricted Use

Under FIFRA, hazardous pesticides may be classified for restricted use and thereby be limited to use only by or under the direct supervision of certified applicators. Certification programs are administered primarily by the states. These programs use various methods to certify applicators after they have proven themselves competent to use restricted pesticides.

The Agency believes that the classification of benomyl for restricted use would not be necessary for every use pattern of the compound; however, use patterns involving aerial application should be considered for retricted use classification. Preventing untrained persons from applying benomyl aerially should significantly reduce the risks to man and the environment caused by misuse or carelessness. Any marginal costs that might result from restriction to certified applicators would be minimal, since state programs to certify applicators are operational in all states; there is little difficulty in obtaining applicator certification and hence, there are many certified applicators. Most aerial applicators are already certified and thus the

adoption of this option would produce very little reduction in risk.

(iv) Require Label Warnings

Under FIFRA, the Agency may require precautionary and warning statements to appear on pesticide labeling. The Agency has assessed the impact of additional cautionary and warning statements with respect to the teratogenic and mutagenic effects and spermatogenic depression caused by benomyl. The warning on a five pound or larger bag would state:

Warning to Workers

The United States Environmental Protection Agency has determined that benomyl causes birth defects and reduced sperm production in laboratory animals. Exposure to benomyl during pregnancy should be avoided. Exposure to benomyl might cause a depressed sperm count. Workers must be sure to wear a cloth mask while mixing benomyl for aerial application. In case of accidental spills or other unusual exposure, cease work immediately and follow directions for contact with benomyl.

The Agency believes that some reduction in risk will be achieved by the education of the user about the potential adverse reproductive effects of benomyl. The cost associated with these risk-reduction measures would be negligible.

3. Option 3: Cancel The Registrations

Adopting this option would indicate that the Agency concludes that the risks associated with certain uses of benomyl outweigh the respective benefits and hence that these uses will result in unreasonable adverse effects. The choice of this option would indicate that the Agency is unwilling to tolerate the level of risk associated with these uses. It

would further indicate that the Agency believes the only regulatory option by which an adequate reduction in risk can be achieved without causing unacceptable economic consequences is cancellation. This option would eliminate the risk associated with the use of benomyl on rice, but at a cost to individual growers of approximately $15 million per year. There should be little, if any, impact on the price of rice to the consumer (Gaede, 1979).

This option would not increase the use of alternate chemicals at this time since there are no other chemicals presently registered for the control of these rice diseases.

V. Recommended Regulatory Action

The analysis of the risks and benefits from the continued uses of benomyl indicates that the primary areas for Agency concern and regulatory action are: (1) inhalation exposure and hence risk incurred by mixer/loaders during aerial application, (2) the potential of benomyl as a gene mutagen, and (3) the acute hazard to aquatic organisms which results when benomyl is applied to rice.

The Agency recommends Option 2 as its regulatory action:

Continue Registration of All Uses; Amend the Terms and Conditions of Registration

This option contains several restrictions on the conditions of use, each designed to reduce the risks associated with exposure to benomyl without simultaneously creating the the adverse economic, social, and environmental impacts associated with cancellation (Table V-1).

A. All Uses

1. Require Label Warnings

This option will educate the user to the potential adverse reproductive effects of benomyl. The Agency recommends this option for all pesticide products containing benomyl packaged in 5 pound or larger bags.

Warning to Workers

The United States Environmental Protection Agency has determined that benomyl causes birth defects and reduced sperm production in laboratory animals. Exposure to benomyl during pregnancy should be avoided. Exposure to benomyl might cause a depressed sperm count. Workers must be sure to wear a cloth mask while mixing benomyl for aerial application. In case of accidental spills or other unusual exposure, cease work immediately and follow directions for contact with benomyl.

2. Additional Mutagenicity Testing

The evidence available to the Agency on the gene mutational potential of benomyl is inadequate to allow the Agency to conclude that there is no human risk attributable to this effect; nor is there clear evidence that such effect does pose a human risk. Additional gene mutation studies will enable the Agency to determine if the use of benomyl will cause unreasonable adverse effects to man or the environment because of its potential to change point mutations. The Agency will require additional tests in this area. Specific requirements will be directed to the manufacturers by the Order.

B. Aerial Application

Pesticide products containing benomyl with directions for aerial application require the following restrictions:

1. Water-Soluble Packaging

The greatest level of exposure to benomyl from any of its uses is to the mixer/loader for aerial application. This exposure mainly occurs during the process of opening the bag containing the benomyl wettable powder and mixing the solution. To lessen this exposure, this option would require that all packages containing five or more pounds be packaged in water-soluble bags as soon as technically feasible.

2. Protective Clothing

The Agency believes that the risk to mixer/loaders can be reduced to an acceptable level if protective clothing is worn. A cloth mask of fine weave must be worn during mixing and loading for aerial application of benomyl if the pesticide is not in water soluble packages.

This reduction in risk can be accomplished with little, if any, economic impact, since applicators are likely to have a cloth mask of fine weave either at their disposal or readily available to them. Therefore the Agency recommends this option.

C. Rice Use

1. Reduce Rate of Application

Application of benomyl on rice results in residues in water that is drained from the rice fields and that eventually reaches fish-bearing streams. These residues present a hazard to aquatic organisms.

DuPont submitted information demonstrating that the lower rate used in Texas would not be efficacious in the other rice growing areas (du Pont, 1979). This option also would not result in the elimination of the hazard to all aquatic organisms and thus is not recommended.

2. Monitoring Studies

The evidence available to the Agency on the potential hazard to aquatic organisms is inadequate to allow the Agency to conclude that no risk attributable to this effect exists. Additional monitoring studies will enable the Agency to further quantify the potential hazard to aquatic organisms. The Agency will require additional studies in this area. Specific requirements will be directed to the manufacturers by the Registration Division.

D. Conclusions

In summary, the Agency recommends continued registration for all uses of benomyl with the following terms and conditions: (1) additional gene mutation studies will be required for all uses; (2) when sold in five pound or larger

packages with directions for aerial application, benomyl should be packaged in water-soluble bags as soon as technically feasible, (3) a cloth mask will be required during mixing and loading for aerial application if the product is not packaged in water-soluble bags, (4) a monitoring study on the fate of benomyl in the environment is required for the continuation of the registration for the rice uses, and (5) additional precautionary labeling will be required. The impacts of the recommended options appear in Table V-1.

TABLE V-1 . Risks/Benefits Matrix

IMPACTS OF REGULATORY OPTIONS SELECTED

REGULATORY OPTIONS	ENVIRONMENTAL RISKS	HUMAN RISK	ECONOMIC IMPACT	ISSUES
1. REGISTER ALL USES AMEND CONDITIONS FOR REGISTRATION				
A. REQUIRE MONITORING STUDY ON RICE USE	RISK LEVEL UNCHANGED	RISK LEVEL UNCHANGED	COST TO MANUFACTURER FOR MONITOR STUDY	FATE OF BENOMYL IN RICE FIELDS UNKNOWN AT PRESENT
B. REQUIRE PROTECTIVE CLOTHING FOR MIXER/ LOADERS (CLOTH MASK)	RISK LEVEL UNCHANGED	INHALATION RISKS ARE REDUCED	PRODUCTION AND QUALITY MAINTAINED AT PRESENT LEVELS FOR THESE USES	EXPOSURE TO APPLICATORS CAN BE REDUCED GROWERS WOULD NOT NEED TO PURCHASE NEW SAFETY EQUIPMENT
C. REQUIRE WATER SOLUBLE PACKING FOR 5 POUND AND LARGER PACKAGES OF BENOMYL	RISK LEVEL UNCHANGED	DERMAL RISKS ARE REDUCED. INHALATION RISKS ARE REDUCED.	PRODUCTION AND QUALITY MAINTAINED IMPACT WOULD BE ABOUT $0.60 PER ACRE	EXPOSURE DURING MIXING CAN BE REDUCED BY 90% PASSIVE METHOD OF REDUCING EXPOSURE. TEST-MARKETING ALREADY IN PROGRESS
D. REQUIRE ADDITIONAL GENE MUTATION TESTS	RISK LEVEL UNCHANGED	RISK LEVEL UNCHANGED	COST TO MANUFACTURER ($9,000-13,000)	TESTS NECESSARY NECESSARY TO DETERMINE RISKS
E. REQUIRE ADDITIONAL PRECAUTIONARY LABELING	RISK LEVEL UNCHANGED	RISK LEVEL REDUCED	COST TO MANUFACTURER FOR LABEL CHANGES	WARNS CONSUMER OF RISKS

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Appendix I

FINAL EXPOSURE ANALYSIS FOR BENOMYL

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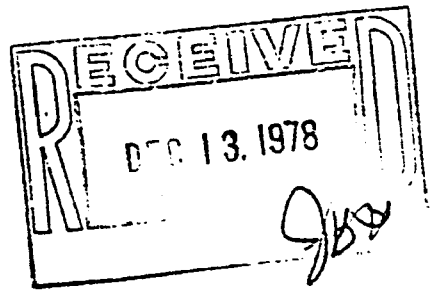
November 28, 1978



I. Introduction

Benomyl, methyl 1-(butylcarbamoyl)-2-benzimidazole carbamate, is a fungicide marketed under the trade name Benlate^{R} (EPA Registration No. 352-354-AA). This systemic fungicide is used to control a variety of pathogenic fungi on crops such as apples, roses, peaches, soybeans, etc. (See label-Appendix A). Benlate is sold under only one label as a 50% A.I. wettable powder with directions for spray application on various crops. Benomyl rapidly converts to MBC (methyl 2-benzimidazolecarbamate) which is generally considered to be the species which provides fungicidal activity (1).

II. Use Practices

Benomyl is applied as a foliar spray on vegetables, fruits, etc. by ground rig, air blast equipment, hand spraying, and aerially. An agitated spray tank is needed to maintain a homogenous suspension. It is also applied in combination with a spray oil to stone fruits, and apples. Applications are made at various intervals (about 7-14 days) or as needed. Benomyl is added to a wax dip for fruit to prevent fungal attack and as a dip for pineapple seed pieces. Exposure from these dip residues are accounted for in food residues. Specific use practices for benomyl are described in section V 9.

III. Recommended Mixing and Use Dilutions (2)

Aerial Application

Crop	Product A.I. lbs/acre	Dilution(gal.)	Maximum Spray Concentration % w/w
Almonds	0.5-0.75	10-20	0.9
Avacados	0.5-1.0	10-20	1.2
Beans	0.75-1.0	10-20	1.2
Cabbage	1.0	5-10	2.4
Cucurbits	0.25	5-10	0.6
Grapes	0.5-0.75	15-20	0.6
Peanuts	0.18-0.25	5-10	0.6
Pecans	0.5	10-20	0.6
Rice	0.5-1.0	3-10	4.0
Stone Fruits	0.375-0.75	10-20	0.6
Strawberries	0.5	10-20	0.6
Soybeans	0.25-0.5	3-10	2.0
Sugar Beets	0.18-0.25	5-10	0.6
Trees, Flowers, etc.	0.25-0.5	20	0.3
Ground Spray			
Almonds	0.5-0.75	*	*
Apples	0.125-0.18	200-500	0.0125
Avacados	0.4-1.0	*	*
Beans	0.75-1.0	*	*
Celery	0.125-0.25	*	*
Citrus	0.75-1.5	*	*

Ground Application Continued

Crop	Product A.I. lbs/acre	Dilution(gal.)	Maximum Spray Concentration % w/w
Curcurbits	0.125-0.25	*	*
Grapes	0.5-0.75	*	*
Macademia Nuts	0.875	*	*
Mangoes	0.5-1.0	*	*
Mushrooms	0.5	100	0.06
Peanuts	0.18-0.25	*	*
Pears	0.125-0.18	*	*
Pecans	0.25-0.5	*	*
Rice	0.5-1.0	*	*
Soybeans	0.25-0.5	*	*
Stone Fruits	0.375-0.75	*	*
Strawberries	0.5	*	*
Sugar Beets	0.18-0.25	*	*
Tomatoes	0.25-0.5	100	0.06
Roses, Flower, etc.	0.25	100	0.03
Bulbs (dip)	0.83	100	0.1

*Recommended dilution not provided

IV. Assumptions

1. The spray concentrations listed in III are in common use.
2. An applicator weighs 60 kg.
3. Equipment used to apply benomyl and applicator protection are comparable to examples used by Wolfe and Durham (3) in their calculation of worker exposure to pesticides.
4. Label directions are followed.

V. Unit Exposure for Benomyl

The main volume of the approximately 3 million pounds of benomyl used in 1977 was for control of fungi on the following crops(4):

Crop	Total lbs ai Used
Soybeans	761,000
Stone Fruits	344,000
Rice	299,000
Citrus	259,250
Bananas	200,000
Grapes	173,692
Peanuts	158,500
Vegetables	151,500

Turf	150,000
Ornamentals	125,000
Pecans	100,000
Apples	96,184
Berries (Strawberries, Blueberries, Rasberries	71,911
Sugarcane	26,000
Sugar Beets	13,500
Wheat	11,150
Mushrooms	11,034
Pears	10,928
Elm	7,010
Mangoes	6,000
Avocados	1,628
Pineapples	1,506
Macadamia Nuts	100
Total	3,043,387

This exposure analysis will provide an estimate of exposure related to benomyl application on most of the above crops by air and by ground spray equipment and include other minor uses.

1. Exposure to mixer/loaders

This group according to Jegier (5) receive relatively high levels of exposure since they handle the concentrated product. During this operation the product is transferred to a spray tank or other container and water is added. During this time, dermal and inhalation exposure can occur. Jegier found that while loading 25% Guthion WP, an applicator received a dermal exposure of 53 mg/hr and 1.27 mg/hr inhalation exposure (mean values). To estimate exposure for benomyl in an analogous case, a factor needs to be considered to arrive at a comparable estimate.

Since benomyl is twice as concentrated, the exposures recorded should multiplied by two:

Dermal exposure:

53 mg/hr X 2/60 kg = 1.8 mg/kg/hour.

Inhalation exposure:

1.27 mg/hr X 2/60 kg = 0.04 mg/kg/hr.

2. Exposure Via Air Blast Spraying in Orchards

Wolfe and Durham (2) found that applicators applying pesticide spray in apple orchards with power spray equipment received exposure in the range of 15-50 mg/hr dermal and 0.02-0.1 mg/hr inhalation. They found that the mean values for this application method were 30 mg/hr dermal and 0.04 mg/hr by inhalation.

Dermal exposure: 30 mg/hr/60 kg = 0.5 mg/kg/hr

Inhalation exposure: 0.04 mg/hr/60 kg = 0.0007 mg/kg/hr

3. Exposure Via Hand Spraying on Vegetables

Wolfe and Durham (3) found that handspraying of vegetables can lead to exposure. With an applicator applying 0.09% parathion, an exposure of 9.1 mg/hr dermal and 0.29 mg/hr by inhalation was recorded. Since the parathion spray is about one-third more than the recommended benomyl spray (0.06%), an estimate of exposure to benomyl can be made by incorporating a factor of 0.66.

Dermal exposure: 9.1 mg/hr X 0.66 (factor)/60 kg = 0.1 mg/kg/hr

Inhalation exposure: 0.29 mg/hr X 0.66 (factor)/60 kg = 0.003 mg/kg/hr

DuPont, in Vol. 2 (Appendix 20) of their rebuttal document provided measurements of applicator exposure to benomyl from hand spraying vegetables. In the experiment, three different applicators treated vegetables with recommended spray dilution. The results (averaged) indicate an average of 2.2 mg/hr dermal and 0.015 mg/hr inhalation exposure. This compares well with the extrapolation from the measured parathion exposure (adjusted for concentration difference) of 6.0 mg/hr dermal and 0.2 mg/hr. Since DuPont's data is based on actual use of benomyl, their data will be used to estimate exposure.

Dermal exposure:

2.2 mg/hr/60 kg = 0.04 mg/kg/hr

Inhalation exposure:

0.015 mg/hr/60 kg = 0.0003 mg/kg/hr

4. Ground Boom Spraying of Vegetables

According of Wolfe and Durham (2), exposure to workers applying 0.09% parathion spray with a ground boom sprayer, received 4.7 mg/hr dermal exposure and .01 mg/hr inhalation exposure. Since benomyl, as used on tomatoes at 0.06%, is applied at about two-thirds the parathion rate, an estimated exposure to benomyl can be calculated.

Dermal exposure: 4.7 mg/hr X 0.66 (factor)/60 kg = 0.052 mg/kg/hr

Inhalation exposure: 0.01 mg/hr X 0.66 (factor)/60 kg = 0.0001 mg/kg/hr.

5. Exposure to Pilot-Aerial Application

A typical application of benomyl to beans calls for one pound of benomyl diluted to 10 gallons (1.2% w/w) applied over one acre.

Jeiger (5) measured the exposure of a pilot during application of 0.6 pounds endrin (A.I.) per gallon (7.1% w/w) to 27 acres or one pound/acre (same as benomyl). By analysis of respirator pads and collector pads on the pilot's skin, he found pilots were exposed to 1.18 mg/hr dermally and 0.08 mg/hr by inhalation.

Dermal exposure: 1.18 mg/hr/60 kg = 0.02 mg/kg/hr

Inhalation exposure: 0.08 mg/hr/60 kg = 0.001 mg/kg/hr.

6. Exposure from Drift

In aerial application of endrin to cotton and wheat, drift exposure to persons in the vicinity of application was estimated (5). At At 0.4 pounds/acre, measurements of dermal exposure were made for persons at different distances from the application site. By correcting for the difference in the amount of pesticide applied per acre (one pound benomyl per acre) an analogous exposure estimate can be made. Since one pound per acre is 2.5 times 0.4 pounds per acre, the exposure for endrin has been multiplied by this factor to estimate exposure to benomyl. The results are listed in Table I.

Table I

Estimated Dermal Exposure to Benomyl

Distance Downwind		
Feet	Meters	Dermal Exposure mg/kg/ spray incident
83	25	0.04
149	45	0.02
314	96	0.01
644	196	0.004
1304	398	0.002

In a related exposure case Caplan et al. (6) determined the dermal exposure to person directly beneath a spray application. In this case the application rate was 0.46 pounds malathion per acre. Since this rate is lower, an estimate can be made for benomyl exposure at 1.0 pounds per acre by multiplying the observed exposure of 3.6 mg by (1.0/.46) 2.17 to arrive at 7.8 mg/incident (no time period was provided). Therefore, dermal exposure would be 7.8 mg/60 kg or 0.13 mg/kg.

7. Exposure to Flaggers

Flaggers are personnel used to direct the spray swaths of the aerial applicators; as such, they are in close proximity to the spray. Wolfe (2) measured dermal and respiratory exposure to flaggers in orchards being sprayed with 9% parathion. He found an average

exposure for these flaggers to be 84 mg/hr dermal and 0.02 mg/hr by inhalation. As in example #5, benomyl is used at 1.2% spray. To relate this rate to a 60 kg flagger, the following calculation of exposure can be made:

$$\frac{84 \text{ mg/hr}}{60 \text{ kg}} \times \frac{1.2}{9.0} = 0.19 \text{ mg/kg/hr}$$

$$\frac{0.02 \text{ mg/hr}}{60 \text{ kg}} \times \frac{1.2}{9.0} = 0.00004 \text{ mg/kg/hr}$$

8. Exposure Via Benomyl Residues in Food*

To obtain an estimate of benomyl in the diet, the following assumptions were made:

a. Residues of benomyl exist in foods at the allowed tolerance level and include possible post harvest dips.

b. A person consumes an average diet as listed in an EPA memo giving amounts and kinds of food (7).

* The Residue Chemistry Branch has prepared a more comprehensive report on dietary exposure which will be submitted separately.

Benomyl Residues Consumed

Food Item	Tolerance mg/kg (8)	Average consumption (7) grams of food/person/day	ug benomyl consumed/day
pineapple	25	5.87	147
apricots	15	2.23	33
nectarines	15	0.59	9
cherries	15	2.03	30
peaches	15	7.82	117
plums	15	2.63	40
grapes	10	9.72	97
mushrooms	10	0.59	6
berries	7	3.54	24
apples/pears	7	55.19	386
rice	5	10.94	55
strawberries	5	3.65	18
tomatoes	5	6.97	35
celery	2	5.97	12
beans	2	40.42	81
almonds	1	0.59	0.6
avocados	1	0.59	0.6
cucumber	1	14.38	14
melons	1	39.69	40
pumpkin/squash	1	2.23	2
peanuts	.2	7.09	1
soybeans	.2	18.19	4
diary/meat	.1	841	84
			1236.2

Average daily intake is 1.2 mg/day or 1.2/60 kg = 0.02 mg/kg body weight/day

9. Use Patterns and Applicator Exposure

The pesticide benomyl has about 25 distinctive uses as identified by the USDA assessment team (4). Using their estimates of workers and hours involved, and estimating applicators/hours (when not given) by pounds of benomyl used, an estimate can be made of the number of persons exposed to benomyl, and using the exposure estimate generated in Section V (unit exposure), an estimate of their yearly exposure can be made. In some cases only incomplete data are available necessitating assumptions. The following table is a compilation of these uses along with estimated exposure.

It should be noted that data assumes the person involved in application of benomyl does not wear protective clothing or a respirator. It is assumed that an unprotected applicator wears a short-sleeved open shirt, no hat or gloves, and the proportion of skin exposed to that if protective clothing is worn is about 5 to 1; therefore, dermal exposure could be reduced by about 80% if such clothing was worn. A respirator could reduce respiratory exposure to zero. The following data represents a compilation of applicator use pattern (4) and estimates of exposure in V 1-8. It should be noted that some numbers (marked with an E) are estimates based on acreage treated/pounds of benomyl used/typical application times and frequency as stated in the USDA report (4).

8. Use Patterns and Applicator Exposure

	Use Pattern	Exposed Group	Number	hrs/ day	days/ yr	hrs/ yr	Exposure-mg/kg Dermal hr	Dermal day	Dermal year	Inhalation hr	Inhalation day	Inhalation year
1.	Rice (aerial)	Pilots	80	3	10	30	0.02	0.06	0.6	0.001	0.003	0.03
		mix/loaders	200	6	10	60	1.8	10.8	108.0	0.04	0.24	2.4
		flaggers	300	6	10	60	0.19	1.14	11.40	0.00004	0.00024	0.0024
2.	Soybeans (aerial)	pilots	200	3	15	45	0.02	0.06	0.9	0.001	0.003	0.045
		mixer/loader	500	6	15	90	1.8	10.8	162.0	0.04	0.24	3.6
		flaggers	700	6	15	90	0.19	1.14	17.10	0.00004	0.00024	0.0036
3.	Stone Fruits (aerial)	pilots	120	3	40	120	0.02	0.06	2.4	0.001	0.003	0.12
		mixer/loaders	300	6	40	240	1.8	10.8	432.0	0.04	0.24	9.6
		flaggers	240	6	40	240	0.19	1.14	45.60	0.00004	0.00024	0.0096
4.	Stone Fruits (airblast)	applicators (commercial)	60	7	40	280	0.5	3.5	140.0	0.0007	0.005	0.2
5.	Stone Fruits (airblast)	applicators (private)	3000	8	6	48	0.075	4.0	24.0	0.0007	0.006	0.034
6.	Grapes (aerial)	pilots	20	3	5	15	0.02	0.06	0.3	0.001	0.003	0.015
		mix/loaders	40	8	5	40	1.8	14.4	72.0	0.04	0.32	1.6
		flaggers	50	8	5	40	0.19	1.52	7.60	0.00004	0.00032	0.00016
7.	Grapes (airblast)	applicators (commercial)	60	3	20	60	0.5	1.5	30.0	0.0007	0.002	0.04
8.	Grapes (airblast)	applicators (private)	40	4	15	60	0.5	2.0	30.0	0.0007	0.003	0.04
9.	Berries (aerial)	pilot	15	3	22	66	0.02	0.06	1.32	0.001	0.003	0.066
		loaders/flaggers	20	5	22	110	1.8	9.0	198.0	0.04	0.2	4.4

8. Use Patterns and Applicator Exposure

	Use Pattern	Exposed Group	Number	hrs/ day	days/ yr	hrs/ yr	Exposure-mg/kg Dermal hr	Dermal day	Dermal year	Inhalation hr	Inhalation day	Inhalation year
10.	Berries (airblast)	applicators (commercial)	28	3	196	588	0.5	1.5	294	.0007	0.002	0.4
11.	Berries (ground)	applicators (private)	210	3	20	60	0.05	0.15	3.0	0.0001	0.0003	0.006
12.	Fruit Crops (aerial)	pilots	20	3	50	150	0.02	0.06	3.0	0.001	0.003	0.15
		mix/loaders	40	8	50	400	1.8	14.4	720.0	0.04	0.32	16.0
		flaggers	50	8	50	400	0.19	1.52	76.0	0.00004	0.00032	0.016
13.	Fruit Crops (airblast)	applicators (private)	21,000	6	12	72	0.5	3.0	36.0	0.0007	0.004	0.05
14.	Fruit (postharvest	Insufficient information in USDA report. Applicators well protected according to report.										
15.	Citrus (airblast)	applicators	714	8	30	240	0.5	4.0	120.0	0.0007	0.006	0.18
16.	Citrus (post harvest)	According to USDA report, benomyl is used in closed system; hence, no exposure										
17.	Pineapples	applicators	3	According to USDA report, exposure is negligible								

8. Use Patterns and Applicator Exposure

Use Pattern	Exposed Group	Number	hrs/ day	days/ yr	hrs/ yr	Exposure-mg/kg Dermal hr	Dermal day	Dermal year	Inhalation hr	Inhalation day	Inhalation year
18. Sugarcane	According to USDA report, operation is mechanized; hence no exposure										
19. Mushrooms E	applicators	1200	4.5	4	18	0.04	0.18	0.72	0.0003	0.001	0.005
20. Wheat E (aerial)	pilots	10	3	20	60	0.02	0.06	1.2	0.001	0.003	0.06
	mix/loaders	10	7	20	140	1.8	12.6	252.0	0.04	0.28	5.6
	flaggers	10	7	20	140	0.19	1.33	2.660	0.00004	0.0003	0.006
21. Wheat E (ground)	applicators	15	8	15	120	0.05	0.4	6.0	.0001	0.0008	0.012
22. Peanuts	According to USDA, peanut disease fungi have developed resistance; hence, not used now										
23. Turf E (ground)	applicators	200	6	4	24	0.05	0.3	1.2	0.001	0.006	0.024
24. Turf E (handspray)	homeowner	75	0.5	4	2.5	0.04	0.02	0.08	0.0003	0.0002	0.0006
25. Ornamental	applicator (commercial)	Insufficient information, according to USDA report exposure is minimal									
26. Ornamentals	homeowner	534,000	0.5	5	10	0.04	0.02	0.1	0.0003	0.0002	0.0008
27. Vegetables E	all types	1515	2	5	10	0.04	0.08	0.4	0.0003	0.0006	0.003

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8. Code of Federal Regulations Title 40 Protection of the Environment Part 180.294, As Revised July 1, 1976.

Prepared by: Harold R Day

Harold R. Day, Environmental Chemist

Date: December 12 1978

Reviewed and Approved by: for Hoke Hunter Jr.

Chief, Environmental Fate Branch

Date: December 13, 1978

Appendix II

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: April 3, 1979

SUBJECT: Dermal Absorbtion of Benomyl

FROM: Pharmacologist, Toxicology Branch

TO: Christine F. Chaisson
Biochemist, Toxicology Branch

I have reviewed the DuPont paper entitled 2-^{14}C-Benomyl (50% WP) Adsorption Through Rat Skin Part II: Effect of Time and Dose Applied by C.J. Belosco. From the data supplied by this paper one may conclude that it is impossible to obtain a cytotoxic level of 10 ug/ml benomyl in the blood through dermal absorbtion from Benlate® Fungicide 50% WP either dry or in water.

In this DuPont study [2-^{14}C]-benomyl (Benlate® Fungicide) was applied to the shaven skin of rats (200-260 gms) at 0.2, 2.0, 20.0 and 200.0 mg per ~~part~~ rat, 20 rats per dose. Rats were placed in metabolism cages and all urine and feces were collected. Four rats at each dose were sacrificed at 0.5, 1.0, 2.0, 4.0 and 10.0 hours of exposure. Blood samples were collected at sacrifice. Blood concentrations and total urinary excretion of benomyl were determined for each dose at each time of exposure. No attempt was made to distinguish between benomyl and its metabolites of which MBC is the active cytotoxin.

EPA is concerned with the relationship between dose of benomyl applied to the skin and the maximum blood concentration of benomyl-MBC which results therefrom. Figure 1 of the DuPont paper presents this data plotted by dose as hours after treatment against blood concentration of Benomyl. Each point represents the mean of four animals. For each dose a maximum blood concentration of benomyl is reached after four hours of exposure. The highest mean concentration is .070 ppm (70 nanograms per ml) at a 200 mg dose while the highest single rat concentration is .098 ppm (98 nangrams per ml). at the same dose and time. This represents approximately one 80th of the dose considered inactive by EPA but with the data as presented in Figure one it is impossible to determine if the no-effect concentration of 8 ug/ml can be reached by increasing the dermal dose.

In the second figure, I have plotted the same data by hours after treatment as dose against blood concentration of benomyl. Again each point is the mean of four animals. In this figure the doses are plotted on a logrithmic scale in which the intervals are equal for each 10 fold increase of dose. This is a standard procedure in pharmacology for obtaining an S-shaped dose response curve. The line for 0.5 hours indicates that a maximum blood concentration in the order at 35-40 ppm will be reached with increased dermal dose and that skin penatration is time limited at this interval. The remaining lines represent only approximatly the first half of the dose-response curve and it is impossible to determine their limits and whether they will be time or permability limited from the data of this study. However, one may make certian extrapolations from these lines and determine whether it is physically possible to reach the no-effect level of 8 ug per ml in blood. The central portion of a dose-response curve plotted in this fashion is linear. Based on the physical-chemical properties of benomyl and of the skin one can expect no further increase in rate of penetration of benomyl once the linear portion of the dose-response curve is reached as long as we continue to utilize the dry powder or its water form. We also know that a limit in penetration rate will be reached as noted above for the 0.5 hours exposure. We are thus justified in making a linear extrapolation of the dose-response curve as shown by the dashed lines in order to show clearly that a practical limit to benomyl application on the skin is reached far before the concentration of 8 ug/ml in the blood can be reached.

At dose of 2000 mg we estimate an average concentration of 100 ng benomyl in the blood utilizing this extrapolation. Since this means applying 2 grams of benomyl (4 grams Benolate®) to four square inches of rat skin it appears impractical. However, essentially this blood concentration has reached by one rat at a 200 mg dose (98 ng). Therefore, we will extended our extrapolation another unit (to a 20,000 mg dose) in our search for a limit. At a dose of 20,000 mg we estimate an average blood concentration of 130 ng/ml (point 2). At this point we are dealing with an obviously impossible situation. Twenty grams of benomyl (as 40 grams of Benolate®) placed on 4 square inches of a rats back! Only a small portion of the dose is in direct contact with the rats skin and is available for absorption. This is a physical limit to absorption such that the amount absorbed can no longer increase with increased doses. Thus we can conclude that there is an absolute limit to dermal absorption such that a blood concentration of 8 ug/ml cannot be reached.

The possibility of saturation of metabolic and excratory processes appear to be remote but is should be considered. Benomyl is rapidly converted to MBC (the biologically active metabolic) in the mammal. MBC is then inactivated by enzymatic 5-hydroxylation and glucronide or sulfate conjugation in the liver. These compounds are highly polar and are rapidly excreted by the kidneys. These detoxification and excratory processes are of large capacity in the

mammal and one would not expect them to be saturated or even approach saturation by the small concentrations of Benomyl-MBC demonstrated in the blood by these experiments. This lack of saturation is clearly shown in Figure 3 which plots the excretion of benomyl (as $2^{-14}C$ metabolites) against dose for 10 hours of dermal exposure. There is no indication of a full-off of excretion with increased dose and thus no possibility of accumulation due to saturation of the metabolic and excratory processes.

As a final point, one must consider the possibility of bioaccumulation by tissue storage in the mammal. Based on the physical-chemical properties of benomyl and its metabolites and their pattern of excretion, one would not expect benomyl-MBC to accumulate in tissue. The only studies available which bear on this question have been performed and reported by duPont. duPont has reported the results of analytical studies, utilizing C^{14} benomyl, on the blood and testes of rats which received benomyl (a) at a single dose of 1000 mg/kg PO or (b) 10 repeated oral doses of 200 mg/kg/day.

At the 1000 mg/kg dose, total C^{14} residues (calculated as benomyl) ranged from 3 to 13 ug/ml in the blood and from 2 to 4 ug/gm in the testes. At the 200 mg/kg/dose one hour after the last dose there was 1.5 ug/ml in the blood and 0.3 ug/gm in the testes. Twenty-four hours after the last dose no residue was detected (<0.1 ug/gm). These results give no indication of tissue accumulation.

Finally we will consider the application of this information to man. It is generally agreed that human skin is less permeable (by a factor of about five) than the skin of the albino rat. Considering the information presented in the rat dermal absorption study, it is not necessary to consider such a factor and we will simply assume that the human skin is no more permable than the rat skin. Thus we can conclude that exposure of 16% of an individuals skin to a dose of 200 mg will result in a blood concentration of no more than 100 manograms per milliliter.

We can further conclude that an absolute limit to human dermal absortion of benomyl exists such that the no-effect level of 8 ug/ml cannot be reached by dermal abrosption.

Robert Zendzian, Ph.D.

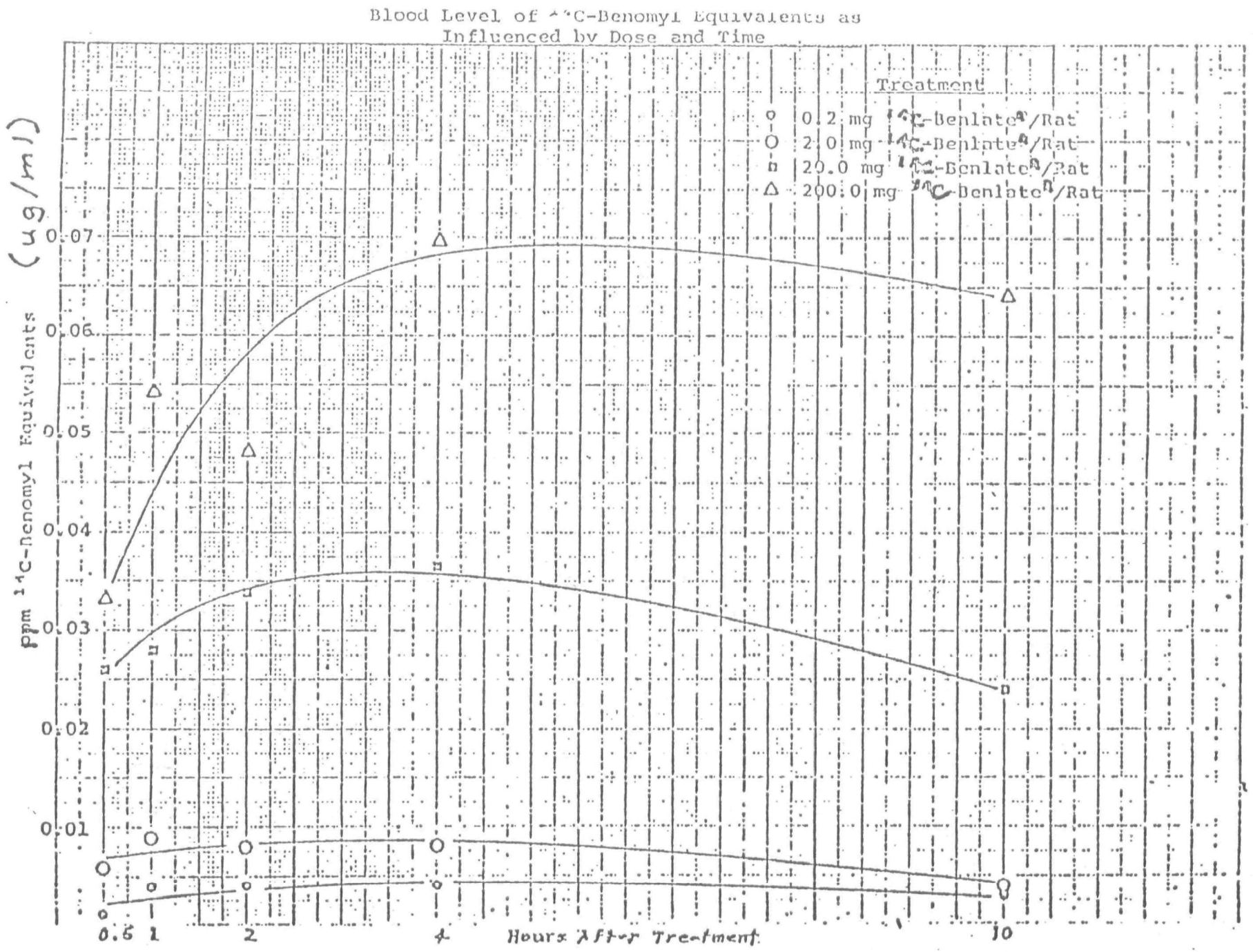

Blood Level of ¹⁴C-Benomyl Equivalents as Influenced by Dose and Time
Treatment
0.2 mg ¹⁴C-Benlate®/Rat
2.0 mg ¹⁴C-Benlate®/Rat
20.0 mg ¹⁴C-Benlate®/Rat
200.0 mg ¹⁴C-Benlate®/Rat
ppm ¹⁴C-Benomyl Equivalents (ug/ml)
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.5
1
2
4
10
Hours After Treatment

Figure 2. Benomyl Dermal Absorbtion Blood Concentrations of $2^{-14}C$ Benomyl and Metabolites mean value of Four rats at each Point

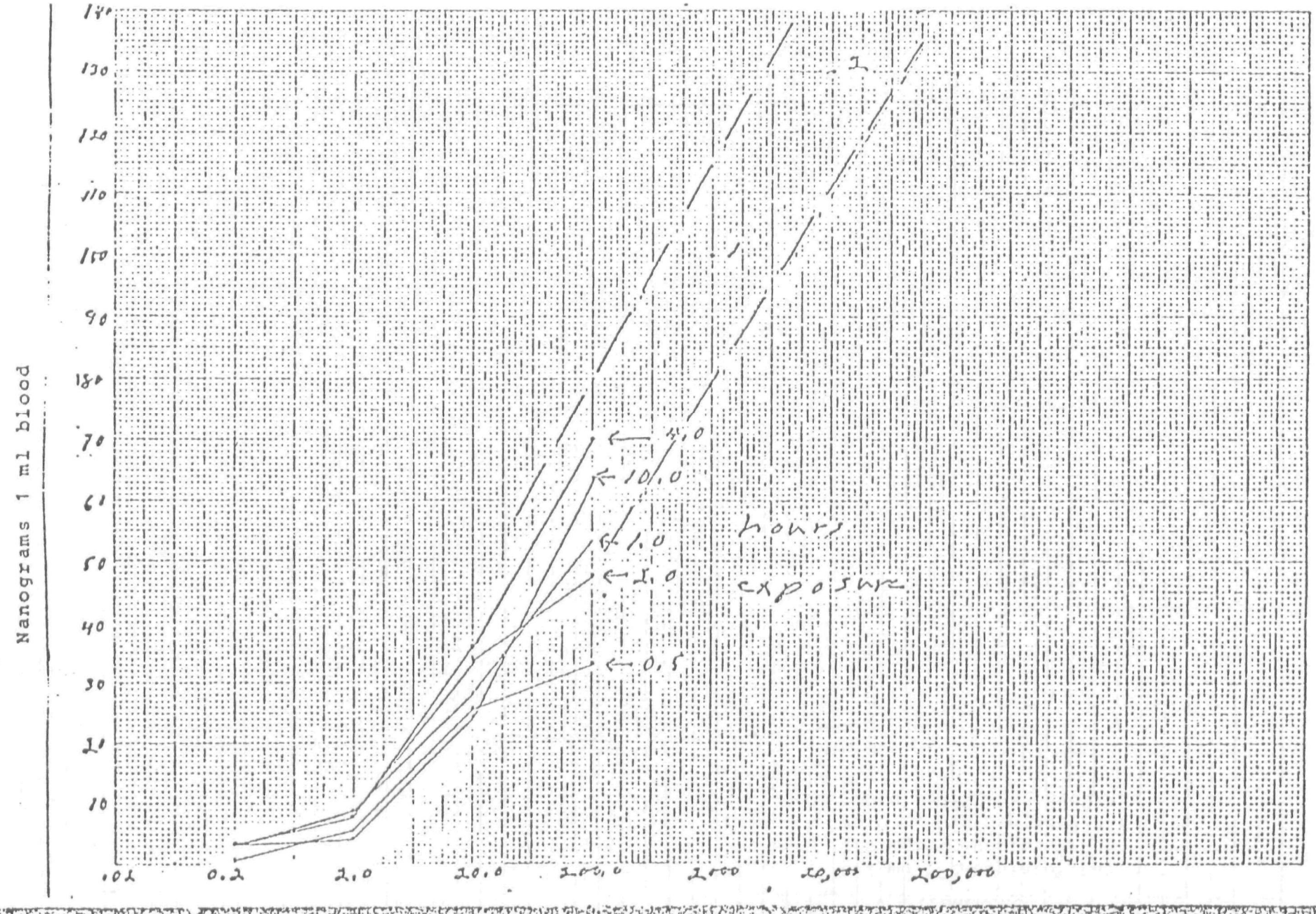
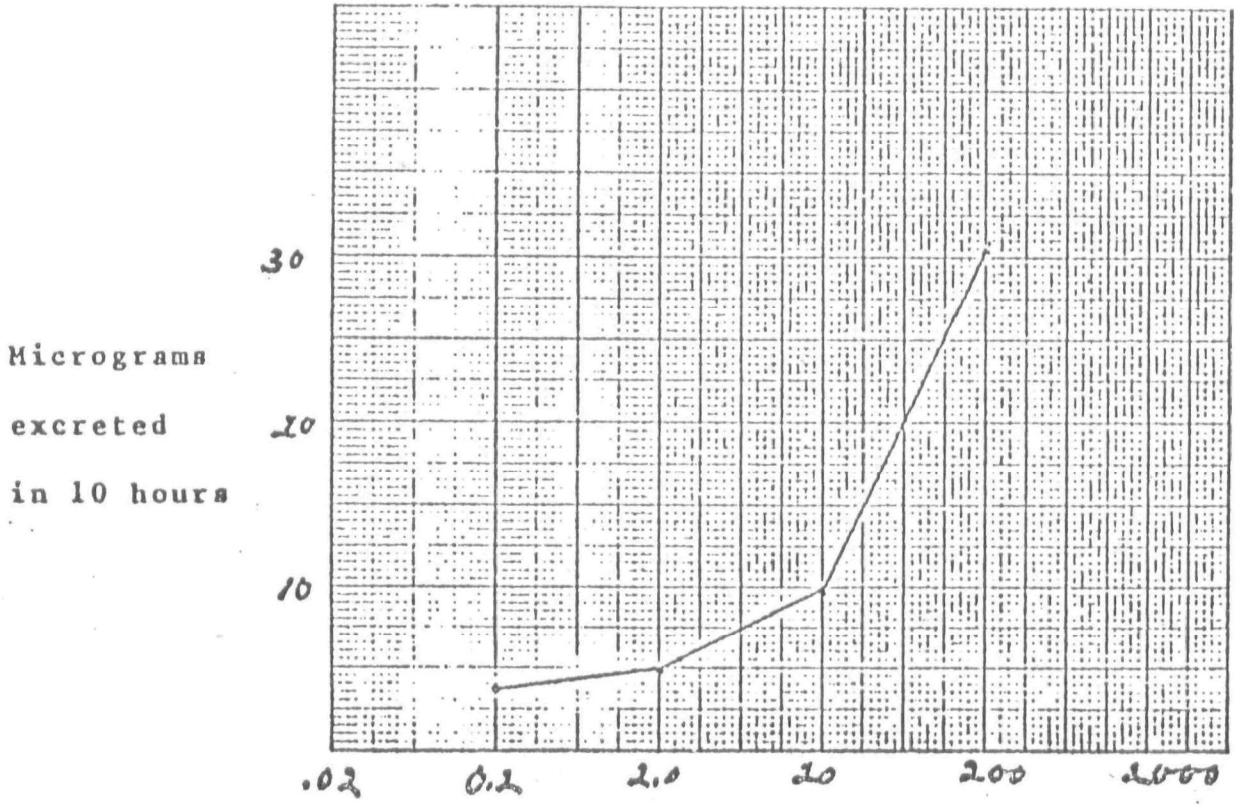
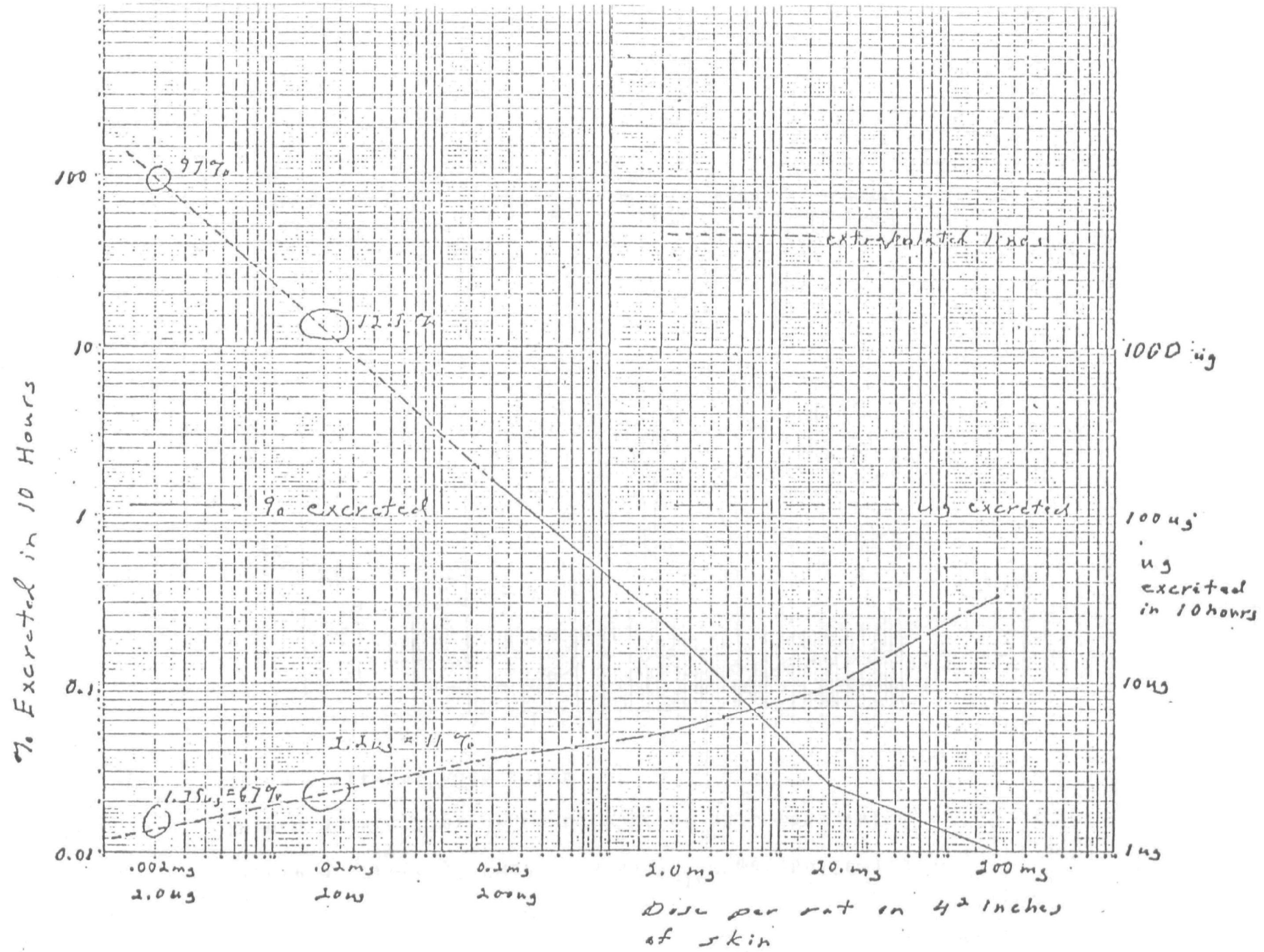
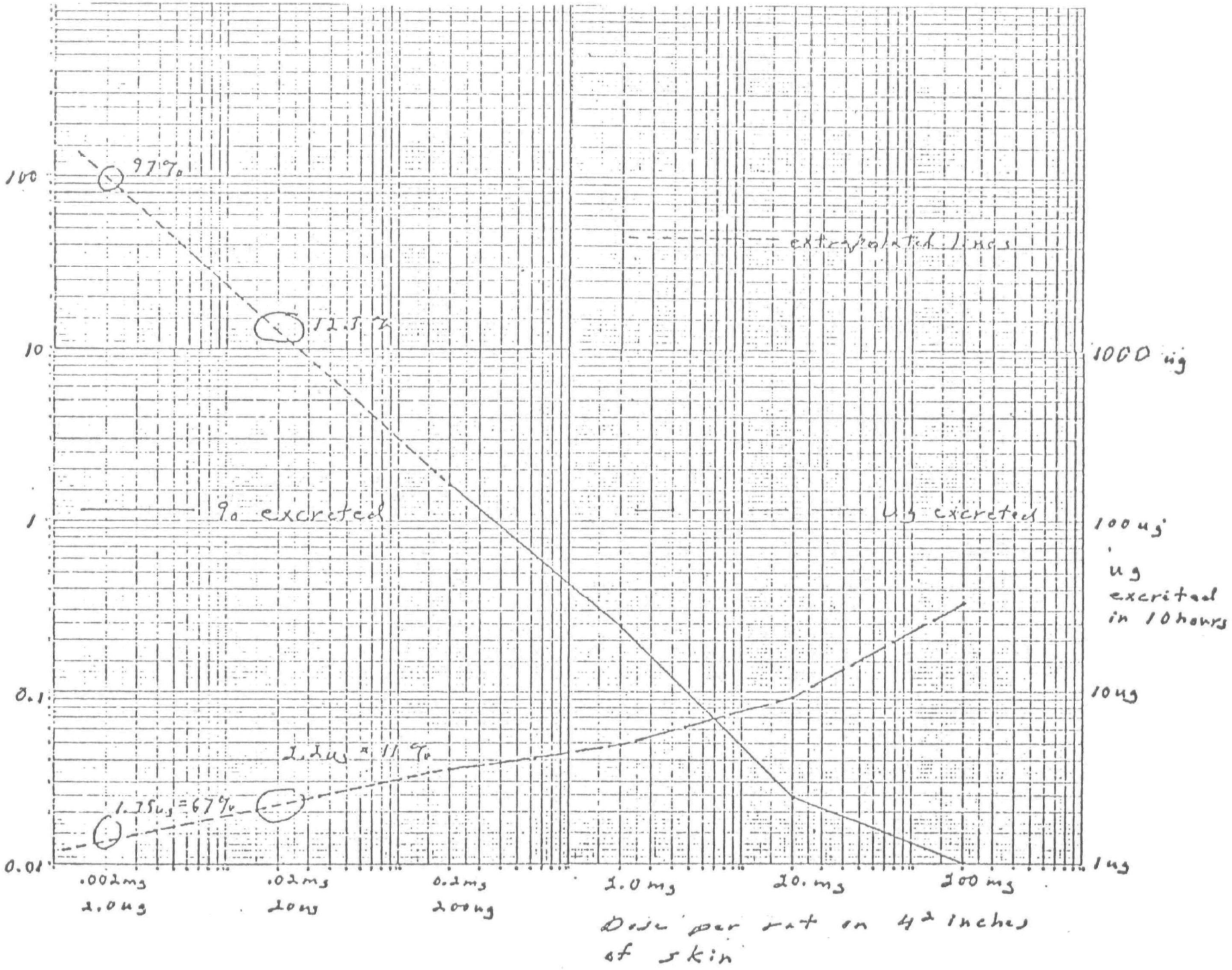


Figure 3. Benomyl Excretion as $2^{-14}C$ metabolites 10 hours dermal exposure to 4^{2} in of skin mean value of Four rats at each point




% Excreted in 10 Hours
100
10
1
0.1
0.01
97%
12.5%
extrapolated lines
% excreted
ug excreted
1.2ug = 11%
1.35ug = 67%
1000 ug
100 ug
ug excreted in 10 hours
10ug
1ug
.002mg
2.0ug
.02mg
20ug
0.2mg
200ug
2.0mg
20.mg
200 mg
Dose per rat on 4² inches of skin


% Excreted in 10 Hours
100
10
1
0.1
0.01
97%
12.5%
extrapolated lines
% excreted
µg excreted
1.2µg = 11%
1.35µg = 67%
1000 µg
100 µg
µg excreted in 10 hours
10 µg
1 µg
.002mg 2.0µg
.02mg 20µg
0.2mg 200µg
2.0 mg
20. mg
200 mg
Dose per rat on 4² inches of skin

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: May 25, 1979

SUBJECT: Dermal Absorbtion of Benomyl Following Human Field Exposure

FROM: Pharmacologist, Toxicology Branch/HED (TS-769)

TO: Christine F. Chaisson
Biochemist, Toxicology Branch/HED (TS-769)

The human dermal absorbtion of Benomyl is calculated as not exceeding 6.23 ug/kg in a worst case dermal exposure of 1.8 mg/kg/hr for 8 hours by a mixer/loader during field application. This estimate is based on dermal absorbtion studies of benomyl performed on the rat by the research laboratories of E.I. duPont de Nemours and Co. It is concluded that the dermal absorbtion of benomyl is in and of itself an insignificant dose during spraying operations and it need not be considered for purposes of exposure calculation.

In a previous memo, (Dermal Absorption of Benomyl, April 3, 1979) I reveiwed the duPont study on the dermal absorbtion of benomyl and concluded that it is impossible to reach a cytototoxic concentration of 10 ug/ml or the no effect concentration of 8 ug/ml of benomyl in the blood following dermal absorbtion. This memo extends that analysis to the estimation of human dermal absorbtion of benomyl during field exposure. The document entitled, Final Exposure Analysis for Benomyl, December 12, 1978 by EFB, HED, OPP, EPA, provides data on dermal exposure to benomyl during various patterns of field use and associated exposure. The worst case of dermal exposure reported involves a mixer/loader who receives 1.8 mg/kg/hour for 8 hours. This exposure is 108 mg/60 kg man/hour on 16% (260^2in) of his surface area.

The data from the benomyl absorbtion study which will be used here consists of two parts 1) the quantity of benomyl excreted with time at various doses and 2) the blood concentrations of benomyl at various doses and times after dosing.

Figure I is a log-log plot of the micrograms benomyl excreted against the dermal dose in millograms applied to 4^2 inches of rat skin. Each line represents a different duration of exposure. This graph can be used to determine the excreted portion of the total amount of benomyl absorbed by four square inches of skin following various doses for various time periods.

The human field exposure data indicates that the mixer/loader was exposed for eight hours and received a 1.8 mg/kg dermal dose for each hour of exposure. This accumulation of dose can be approximated by the line in Figure 2 but this does not truly represent the field situation in which the dosing occurs in bits and dabs nor does it allow use of the rat experimental data in which the entire dose was applied at time zero.

In order to utilize the rat data, I have assumed that 1) the entire hourly dose was applied at the beginning of each hour and 2) that the entire dose remains on the skin for the total subsequent exposure period. This pattern of dosing may be plotted as shown in Figure 3 and will allow use of the rat experimental data to estimate human dermal absorbtion. It must be noted that these assumptions err in overestimating the dermal dose which accumulates, during the duration of exposure and which cannot be expected to stay on the skin for the entire duration of exposure. The calculations involved and results obtained are shown in Table I. The human dose is converted from mg/kg/hr to mg/4^2 in/hr. This figure is used on the one hour line of the graph of Figure I to obtain the ug/kg excreted which represents part of the quality absorbed. The remainder of the quantity absorbed is estimated by using a factor obtained from the blood concentrations of benomyl in the rat at one hour after dermal doses of 2 and 20 mg/4^2 inches of skin.

A 250 gram rat has a blood volume of 6.4% or 16.1 ml. At a dose of 2 mg/rat the average blood concentration of benomyl in four rats at one hour was 9 ng/ml for a total of 147 ng/rat. The quantity excreted was 310 ng for a total quantity absorbed of 457 ng of which the quantity excreted was 68%. At a dose of 20 mg/rat the blood concentration was 28 ng/ml or 451 ng/rat. The quantity excreted was 670 ng/rat for a total quantity absorbed of 1121 ng/rat of which the quantity excreted was 60%. Since the 2 mg and 20 mg doses defined the portion of the excretion curve used to obtain the value in Table I, column three, the mean value of 64% excreted will be used to correct for the quantity retained in the body. The correction gives the values in column five of Table I which are maximum values.

The values in column five of Table I are the total quantity absorbed after each hour of exposure assuming that the rat skin and the human skin are equally permeable to externally applied substances. There is experimentally derived reason to believe that the human skin has only one-fifth the permeability of the rat skin. This skin permeability factor is used to obtain the figures in column six of Table I which are minimum values.

From these calculations it is concluded that a mixer/loader exposed dermally to 1.8 mg/kg/hr of benomyl for 8 hours will absorb no more than 6.23 ug and no less than 1.25 ug of benomyl per kilogram. If the high dose were injected into the blood stream of a 60 kilogram man, it would result in a blood concentration of 1.6×10^{-3} ug/ml. This dose is approximately onefour thousandth of the no effect level of 8 ug/ml. Not only is this an insignificant dose but, intravenous injection will result in a much higher blood concentration then could occur with slow dermal absorbtion of the same amount of benomyl over a period of eight hours.

Robert Benzian, Ph.D.

	Exposure	Absorption				
Hour	mg/4^2 in /hr.	ug/4^2 in /hr.	ug/kg /hr.	ug/kg Σ hr.	+ Blood quantity ug/kg Σ hr.	÷ Human skin permability ug/kg Σ hr.
I	1.66	0.28	0.30	0.30	0.47	0.09
2	3.32	0.36	0.39	0.69	1.08	0.22
3	4.98	0.42	0.45	1.14	1.78	0.36
4	6.64	0.46	0.50	1.64	2.56	0.51
5	8.30	0.50	0.54	2.18	3.41	0.68
6	9.96	0.52	0.56	2.74	4.28	0.86
7	11.62	0.56	0.60	3.34	5.22	1.04
8	13.28	0.60	0.65	3.99	6.23	1.25

Table I. Dermal Absorbtion of Benomyl Following Field Exposure: Mixer/loaders 1.8 mg/kg/hour.

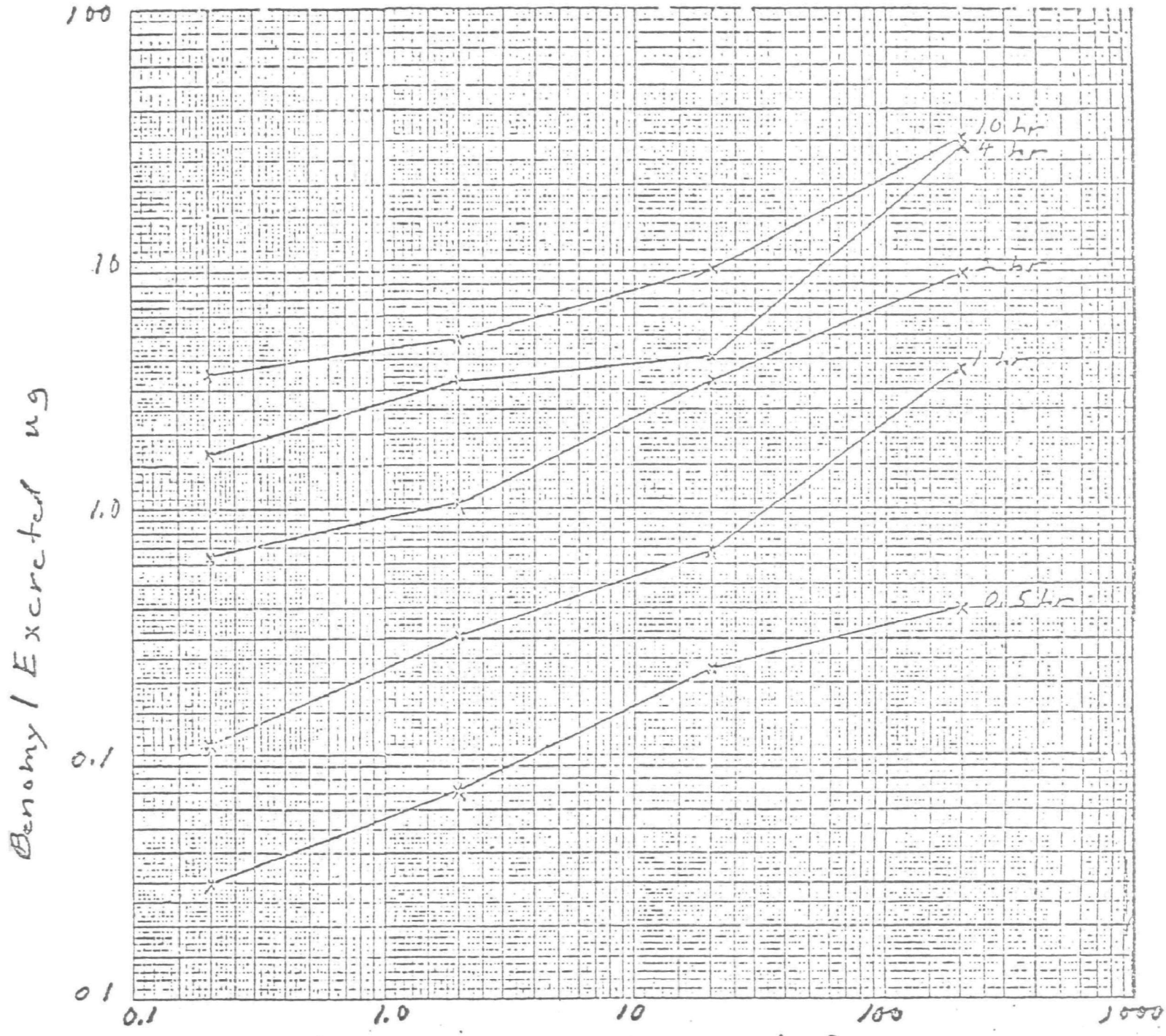


Figure I Benomyl excretion following dermal application to rats. Each line represents a different period of application. Values are average of four rats at each point.

Figure 2

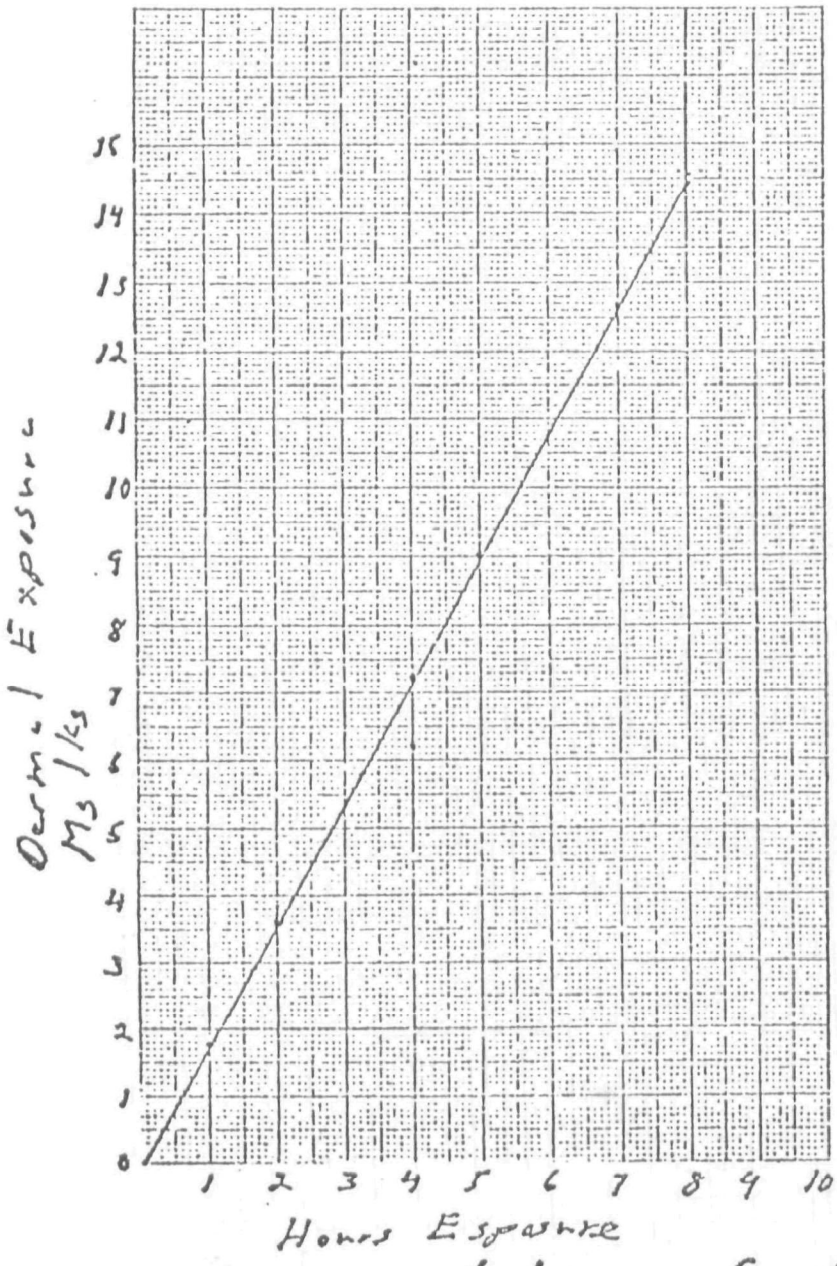
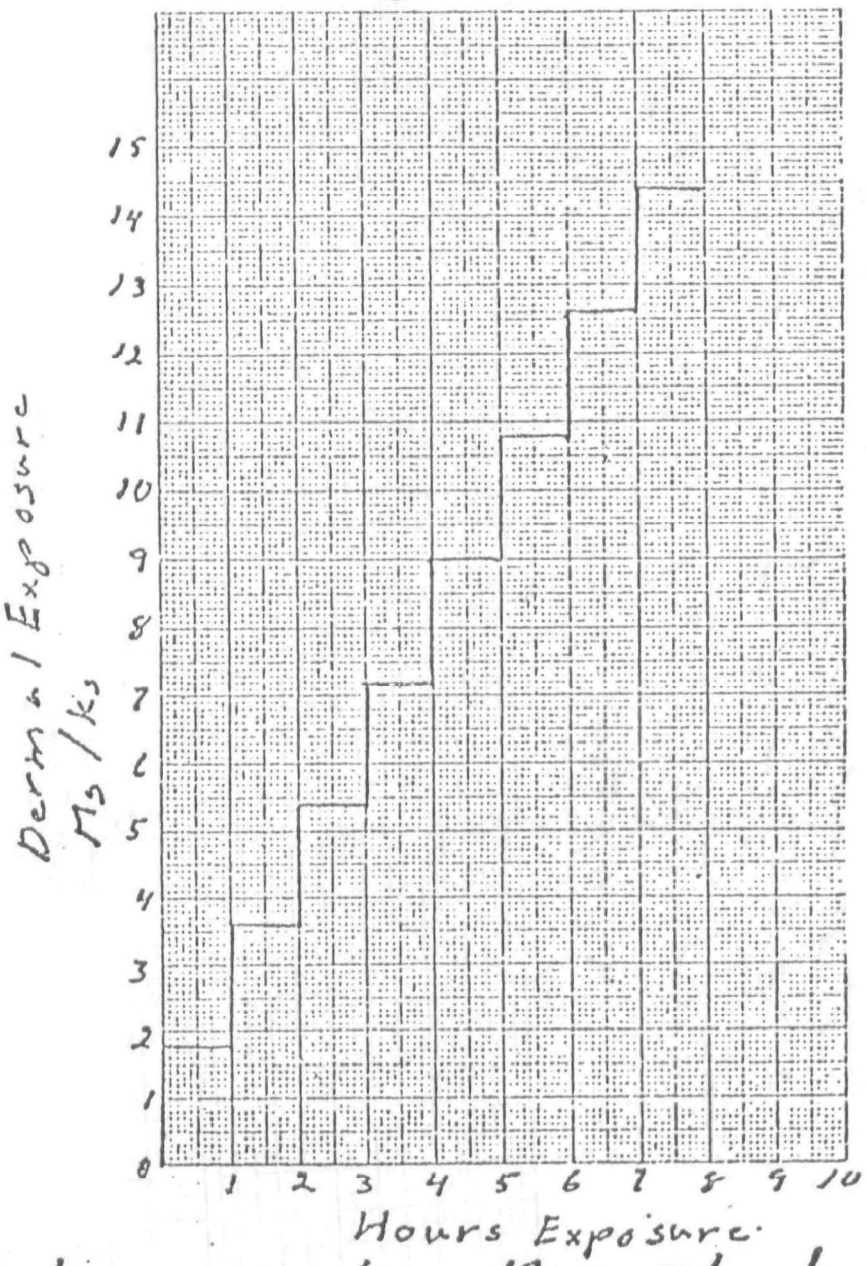


Figure 3



Representations of dermal exposure to a Mixer-Loader