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Office of
Pesticides and Toxic Substances
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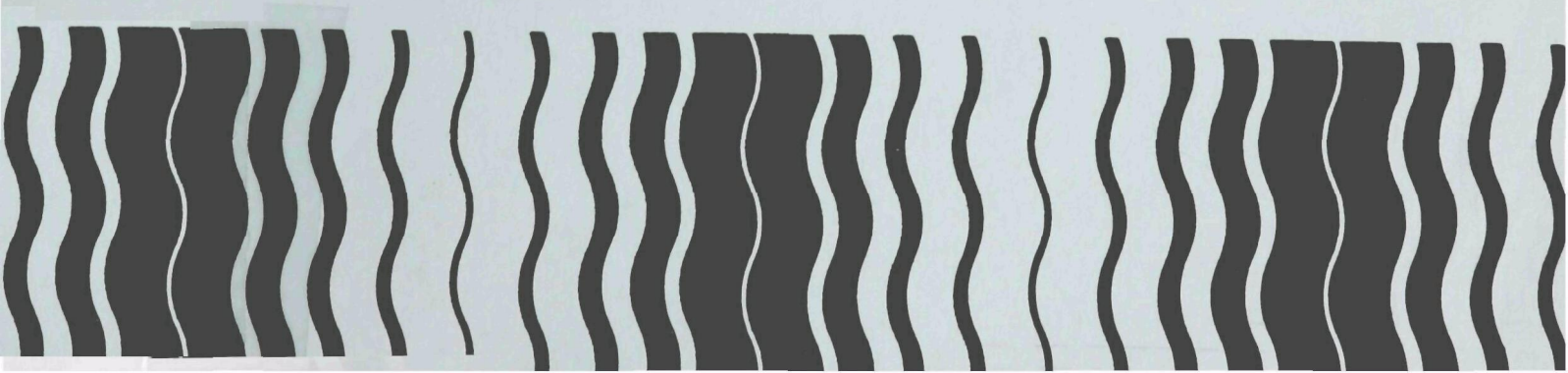
Pesticides

EPA

Captan
Special Review Position Document 2/3



CAPTAN POSITION DOCUMENT 2/3

Office of Pesticide Programs
Office of Pesticides and Toxic Substances
U.S. Environmental Protection Agency
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Washington, D.C. 20460

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ACKNOWLEDGEMENTS

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Executive Summary

On August 18, 1980, the Environmental Protection Agency (the Agency) issued a Notice of Rebuttable Presumption Against Registration (RPAR) and Continued Registration of Pesticide Products Containing Captan (45 FR 54938). That action was based on the Agency finding that registrations of pesticide products containing captan met the 40 CFR 162.11(a)(3) risk criteria relating to oncogenicity and mutagenicity. The Agency at the same time solicited evidence on possible adverse effects of captan regarding fetotoxicity, teratogenicity, hypersensitivity, and acute toxicity to aquatic wildlife.

In the United States, usage of captan is estimated at 9 to 10 million pounds active ingredient per year. According to Agency records, there are approximately 600 EPA registered pesticide products containing captan as an active ingredient. It is applied widely to control fungi on a variety of fruits, vegetables, and ornamental crops; on plant seeds; on food crop packing boxes; in soil before planting; on interior surfaces; in oil-based paints, lacquers, paper, wallpaper paste, plasticizers, polyethylene, vinyl, rubber stabilizers and textiles; and in combination with insecticides on food crops, seed treatments, and household pets. The entire United States population may be exposed to captan residues from these agricultural and non-agricultural uses. Besides these pesticidal uses, there are products registered with the Food and Drug Administration (FDA) containing captan, such as cosmetics and pharmaceuticals.

As part of the Special Review process, the Agency evaluates the risks and benefits associated with the uses of a pesticide and then proposes any regulatory actions necessary to ensure that use of the pesticide does not result in unreasonable adverse effects. Regarding risks, studies conducted on mice and rats have shown statistically significant increases in the incidence of gastrointestinal tumors in mice and kidney tumors in rats. Based on the oncogenic potency demonstrated in these studies and on estimates of human exposure to captan, the Agency assessed lifetime cancer risks from dietary and applicator exposure to captan and exposure to end products containing captan as a preservative. Although captan met the RPAR risk criteria for mutagenicity because it induced gene mutations in some nonmammalian organisms, it has not caused heritable mutagenic effects in mammalian tests. Although captan may cause somatic mutational events, the risk of heritable mutagenicity to humans is low or non-existent and does not warrant further testing at this time.

EPA's risk assessment for reproductive effects indicates that the dietary exposure of the average human is greater than the level calculated to be an acceptable daily intake; however, EPA's final analysis of this risk will depend on the residue data being required of registrants.

Existing data also indicate that captan induced teratogenic effects, such as reduction in fetal weight and fused ribs in hamsters. However, additional data are needed before a definitive judgment can be made. Therefore, EPA is requiring an additional teratology study in hamsters.

Though captan is acutely toxic to fish, there are no aquatic uses for it and leaching is not likely to occur. It is also unlikely to contaminate ground water.

The benefits of captan were assessed in terms of economic impacts which would result if the chemical were withdrawn and users forced to substitute alternatives. For food uses which the Agency is proposing to cancel, moderate impacts would be anticipated in production of apples ($0.9 - $3.3 million), almonds ($1.4 million), strawberries ($5.9 million), peaches ($2.3 - $5.0 million), bushbeans ($3.5 to $4.0 million), apricots ($0.4 - $0.7 million), nectarines ($0.7 million), and in the treatment of seeds (up to $9.2 million). While not quantified, cancellation of home garden uses could result in some increase in disease control costs. For other food uses of captan, the effects would be minor to insignificant. Although the Agency is not proposing to cancel non-food uses of captan, as discussed below, the benefits were assessed assuming that these uses would be withdrawn from the marketplace. For example, there would be moderate economic effects on the ornamental plant industry because of the loss of captan availability for use on carnations and the lack of alternatives ($6 to $12 million). For almost all uses of captan, registered alternatives exist; but these alternatives are usually more expensive. The toxicity data-base for many of these chemicals is incomplete; some chemicals may be more, less, or equally as toxic as captan. Therefore a comparison of their toxicity with that of captan is not possible at present.

In weighing risks and benefits, the Agency reviewed a number of options to reduce risks. For dietary exposure, these included extending preharvest intervals, modifying application practices, reassessing tolerances for captan residues, and prohibiting post-harvest application. However, the available information was insufficient to assess the effectiveness of these measures to reduce risks and consequently additional data are being requested under FIFRA 3(c)(2)(B). For persons applying captan to crops, mixing or loading formulations, working in fields treated with the pesticide, and using end products containing the chemical, the Agency considered requiring use of protective clothing and dust masks or respirators. Such action would reduce exposure by 80 to 90%, depending upon the protective measures utilized.

Based on its analysis of the risks and benefits, the Agency proposes the following regulatory actions. For agricultural applications of captan, these are:

-- to cancel use on all food crops, but to require submission of residue data to determine actual residue levels before setting forth a final determination in Position Document 4. However, in the final decision, the Agency will retain any use where data are submitted that demonstrate that actual residues are sufficiently lower than current tolerances or that modifications to application practices will sufficiently reduce dietary risk.

-- to continue to permit use for seed treatment, but to require submission of residue data to establish seed treatment tolerances and to determine whether the residues, if detectable, are of concern;

-- to continue to allow the feeding of detreated corn seed to cattle and hogs if done at least fourteen days prior to slaughter and if the corn seed residues are less than 100 ppm;

-- to require workers to wear dust masks and impermeable gloves when applying, mixing or loading captan formulations; and

-- to require harvesters and weedpickers to wear water-resistant gloves when working in fields or nurseries in which ornamentals have been treated with captan formulations.

For non-agricultural use of captan, the Agency proposes:

-- that persons incorporating captan into end products such as adhesives, plastics, paints, and cosmetics wear impermeable gloves, respirators (dust masks for cosmetic incorporation), and protective clothing;

-- that labels be amended to require that impermeable gloves be worn when applying oil-based paints for home or professional use; and

-- that labels be amended to require people to wear gloves when washing their pets with animal shampoos containing captan.

The decision to cancel all food uses of captan is based on the conclusion that the cancer risks outweigh the moderate to low benefits. In the absence of acceptable residue data, the Agency based the calculations of dietary risk on established tolerances which represent the highest residues which may legally be present on food crops treated with captan. While the U.S. population may not be exposed to levels as high as this, the Agency had no other valid data on which to base the proposed regulatory action. However, the Agency has required residue data from registrants to be submitted and invites other interested parties to submit relevant data. The Agency believes that the residue data will make possible further refinement of its dietary risk assessment.

The Agency wants to emphasize that it is also concerned about the alternative fungicides to captan. Data available indicate that fungicides, as a class, present toxicological problems. The Agency is also concerned that the proposed regulatory decision regarding food uses of captan may encourage users to switch to alternative chemicals which may also have toxicological problems. The Agency is currently examining or will examine each alternative fungicide in turn either through the Special Review or Registration Standard processes. The Agency encourages registrants to generate data on safer and less toxic chemicals and to develop alternative methods to control fungal infestations on crops.

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I. INTRODUCTION

The Environmental Protection Agency (the Agency) is examining captan because of the oncogenic, mutagenic, teratogenic, and reproductive effects as outlined in the Position Document 1 (PD 1), published in 1980 (45 FR 54938). The Agency is concerned about these adverse effects of captan, as well as the potential effects of alternative fungicides, many of which may also pose risks to human health or the environment. The Agency has reviewed a number of these fungicides either through the Special Review or Registration Standard processes and has taken regulatory actions to reduce risks or require supporting data on these chemicals. The Agency will review the other alternatives so that the data base will be improved and the Agency will be able to make appropriate regulatory decisions.

Data available at this time has led the Agency to conclude that the continued registration for use of captan on food crops and certain other uses would result in unreasonable adverse effects on the environment. However, in the final decision, the Agency will retain any use where data are submitted that demonstrate that actual residues are sufficiently lower than current tolerances or that modifications to application practices will sufficiently reduce dietary risk. Due to a general lack of adequate data, the Agency has had to make a number of "worst-case" risk and exposure assumptions in the development of the risk assessment. The Agency has required the registrants to develop data pursuant to FIFRA 3(c)(2)(B) so that the risk assessment can be refined. In addition, the Agency encourages other interested parties to submit any data that they may have which could be of use to the Agency in the refinement of its risk assessment. All data received by the Agency will be evaluated and incorporated before a final decision is issued in the Position Document 4.

The Agency is also concerned that if captan were cancelled or restricted, users would switch to alternative chemicals that might be as toxic or more toxic than captan. The Agency encourages registrants and users to provide information on methods of reducing dietary and non-dietary exposure to captan. The Agency also encourages registrants to develop data on safer and less toxic chemicals to control fungal infestations or to research and develop safer methods to manage fungal pests. These methods could include non-chemical means of control, safer application methods and practices, and the use of integrated pest management.

A. BACKGROUND

1. Regulatory History

The Federal Insecticide, Fungicide, and Rodenticide Act as amended (FIFRA) and its regulations require the Agency to

review the risks and benefits of the uses of pesticides. On August 18, 1980, the Agency issued a notice of Rebuttable Presumption Against Registration (RPAR) and Continued Registration of Pesticide Products Containing Captan. The Agency had determined that registrations and applications for registration of pesticide products containing captan met or exceeded the 40 CFR 162.11(a)(3) risk criteria relating to oncogenicity and mutagenicity. The Notice also discussed other relevant adverse effects including teratogenic, fetotoxic, and reproductive effects.

The Notice invited comments from the registrants as well as from the public. The comment period lasted 45 days and all rebuttal comments received were evaluated.

2. Organization of this Position Document

This Position Document 2/3 (PD 2/3) addresses the risks and benefits of the uses of captan. This document contains five parts. Chapter I is this Introduction. Chapter II discusses primarily the potential risks of captan use. It includes descriptions and evaluations of the risk information, exposure data, rebuttal submissions and analyses, and the Agency's risk conclusions. It also addresses recent information on reproductive effects, teratogenicity, and metabolism. Chapter III dicusses the benefits of different captan uses, and discusses the assumptions and limits of these estimates. Chapter IV discusses the risks of the alternative pesticides to captan, describes the possible regulatory options to reduce the risks of captan, evaluates the risks and benefits of these regulatory options, and summarizes the regulatory actions which the Agency proposes to take concerning captan.

3. The Special Review Process

Issued under FIFRA as amended (7 U.S.C 136-136y), 40 CFR 162.11 provides that a Rebuttable Presumption Against Registration (RPAR or Special Review) shall be conducted if the Agency determines that a pesticide meets or exceeds any of the risk criteria relating to acute and chronic toxic effects set forth in 40 CFR 162.11(a)(3). In making this determination, the Agency is guided by section 3(c)(8) of FIFRA which directs the Agency to begin a Special Review only if it is based on a "validated test or other significant evidence raising prudent concerns of unreasonable adverse risk to man or the environment." If such a determination is made, the registrant(s) will be notified by certified mail and afforded an opportunity to submit evidence in rebuttal to the Agency's presumption. Alternatively, any registrant may voluntarily petition the Agency to cancel the registration of its product(s).

Following the initiation of the Special Review, the pesticide use or uses of concern will enter the public discussions stage of the Special Review process. Registrants

and interested members of the public may submit written comments, information, or request public discussions on the Agency's proposed actions and/or other proposals for additional or alternative actions. Registrants may submit information indicating that captan does not pose a risk to man or the environment and/or that the benefits exceed the risks associated with captan use. Interested members of the public may submit information concerning the risks and benefits associated with the use of captan.

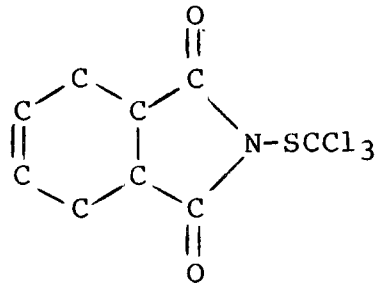
If risk issues cannot be resolved through voluntary actions, the Agency proceeds to evaluate the risks and benefits of the pesticide and to propose a regulatory solution in this PD 2/3 and may submit a proposed Notice of Intent to Cancel to the Scientific Advisory Panel and the Secretary of Agriculture. After obtaining comments from the Scientific Advisory Panel, the Secretary of Agriculture, registrants, and the public on PD 2/3, the Agency would issue a Position Document 4 (PD 4) supporting the Agency's final regulatory position, which may include a Notice of Intent to Cancel pursuant to FIFRA, section 6. If the Agency determines that the risks of use exceed the benefits, the Agency would issue a notice of intent to cancel the registration of products intended for such use. The notice may identify for specific uses certain changes in the composition, packaging, and/or labeling of the product which would reduce the risks to levels that the Agency would consider acceptable. Cancellation would become effective unless within 30 days of issuance of the notice, the registrant either requests a hearing to challenge the cancellation or submits an application to amend his product's registration in a manner prescribed in the notice of intent to cancel.

B. CHEMICAL BACKGROUND

1. Chemical and Physical Characteristics

Captan is the accepted comman name for N-trichloromethyl-thio-4-cyclohexene-1,2-dicarboximide, fungicide, known by the trade names Merpan, Orthocide, Vondcaptan, Vancide-89 and SR-46. It is in the pesticide classification known as dicarb-oximides.

Physically, captan in pure form is an odorless, white, crystalline substance with a melting point of 178°C. The technical grade material is a pungent, yellow to buff, amorphous powder with a melting point of 160°C to 170°C. It is moderately soluble in many organic solvents including chloroform, benzene and dioxane but practically insoluble in water at room temperature. Its empirical formula is $C_9H_8Cl_3NO_2S$, and its structural formula is:



2. Registered Uses and Production

The Agency records show registrations for approximately 600 federally registered pesticide products containing captan as an active ingredient. These registrations are held by 139 registrants. The technical material is produced by Stauffer Chemical Company and Chevron Chemical Company.

Captan was first registered as a pesticide in 1951. The pesticide acts as a protectant against fungal pathogens, and is used extensively as a fungicide: (1) on a wide variety of fruit, vegetable field and ornamental crops, some of which are grown on home and garden sites; (2) on numerous plant seeds; (3) on food crop packing boxes; (4) as a soil preplant treatment; (5) on surfaces inside and outside the home; (6) in dog and cat dusts and shampoos, oil based paints, lacquers, paper, wallpaper paste, plasticizers, polyethylene, vinyl, rubber stabilizer and textiles; (7) in combination with insecticides on food crops, seed treatments, and household pets. It is also registered with the Food and Drug Administration for use in cosmetics and shampoos for humans.

The pesticide products containing captan are most widely used as wettable powders (50-80% active ingredient), flowable (38% active ingredient), and dusts (7.5-15% active ingredient). Other formulations are commercially available as granules.

Approximately nine to ten million pounds of captan are used in the U.S. annually. The six largest crop uses are: apples (2.9 million pounds), peaches (1.1 million pounds), almonds (0.9 million pounds), soybean seed (0.9 million pounds), strawberries (0.7 million pounds) and corn seed treatment (0.7 million pounds).

3. Tolerances

The Agency has established tolerance for captan residues (40 CFR 180.103) in or on these raw agricultural commodities for preharvest uses or for a combination of preharvest and postharvest uses:

(1) 100 ppm - almond hulls, beet greens, cherries[1/], lettuce, spinach;

(2) 50 ppm - apricots[1/], celery, grapes[1/], leeks, mangoes[1/], nectarines[1/], green onions, peaches[1/], plums (fresh prunes), shallots;

(3) 25 ppm - apples[1/], avocados, beans, blackberries, blueberries, huckleberries, cantaloupes, crabapples, cranberries, cucumber[1/], dewberries, eggplants, garlic, grapefruit[1/], honeydew melons[1/], lemons[1/], limes[1/], muskmelons, dry bulb onions[1/], oranges[1/], pears[1/], peppers, pimentos, pineapples[1/], potatoes[1/], pumpkins[1/], quinces, raspberries, rhubarb, strawberries, summer squash, tangerines, tomatoes, watermelons, winter squash;

(4) 2 ppm - almonds, beet roots, broccoli, brussels sprouts, cabbage, carrots, cauliflower, collards, cottonseed, kale, mustard greens, peas, rutabaga roots, soybeans, sweet corn, turnip greens and roots;

(5) 0.25 ppm - taro.

Tolerances for seed and food additives are established in 21 CFR 193.40 for washed raisins (50 ppm) and in 21 CFR 561.65 for detreated corn seed (100 ppm)[2/].

1/ Tolerances reflect both pre- and postharvest use.

2/ Captan is removed from treated corn seed by washing or roasting so that the seed which is left over from planting may be safely fed to hogs and cattle.

II. ANALYSIS OF REBUTTALS AND ASSESSMENT OF RISK

A. REBUTTAL ANALYSIS

1. Risks

The Agency received comments relating to risks in response to the Captan PD 1. Those rebuttals and the Agency's responses to the rebuttals are contained in the following sections on oncogenicity, mutagenicity, teratogenicity/fetotoxicity, and metabolism (Schneider and Burnam, 1984).

a. Oncogenicity

1) Rebuttals by Chevron Chemical Co.

Chevron submitted detailed comments on the oncogenicity of captan, many of which are no longer relevant because new studies, (Chevron mouse study, 1981; Stauffer/Chevron rat study, 1982; and Bio/Dynamics mouse study, 1983) performed since the PD 1 was published, have enabled a more meaningful risk assessment to be performed. Chevron's comments are summarized below.

Comment

Chevron presented an argument concluding that there is no evidence that captan has any oncogenic activity in rats. This was based upon NCI 1977 (Gulf South); Hazleton (Weir 1956 and Dardin 1957); and an interim report of the Stauffer/Chevron (1982) joint study. Chevron argued that the adrenal and thyroid tumors seen in the NCI 1977 study are attributable to spontaneous causes; that the Hazleton study is sufficient to evaluate oncogenicity despite the early deaths; and that the joint Chevron/Stauffer study showed no indication of oncogenic activity during it's in-life portion (only the interim report was avaliable at that time).

Response

The Agency believes that the earlier studies were not as well done as the Chevron/Stauffer rat study (1982) and, now that the final report has been evaluated, the Agency finds evidence of oncogenic activity (statistically significant increase in uncommon kidney tumors in males). The earlier studies are not used in the Agency's risk assessment presented in this PD 2/3.

Comment

Chevron argued that the PD 1 is wrong in stating that captan may cause liver tumors. The argument is based upon (1) limitations of the Innes et al. study (1969), (2) a criticism of the statistical methodology used to support the conclusion of the Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health (1969), and (3) the negative findings of

the NCI (1977) and Chevron sponsored mouse studies (Chevron, 1981 and Bio/Dynamics, 1983) with respect to liver tumors.

Response

The Agency agrees with respect to liver tumors and has not relied on the Innes study in its evaluation of the oncogenicity of captan because the newer Chevron mouse studies show a much higher incidence of other tumors. The NCI 1977 (Gulf South) study showed a higher incidence of duodenal tumors in the mouse. The two registrant sponsored studies (Chevron, 1981 and Bio/Dynamics, 1983) which looked specifically for these normally rare tumors, found them in even higher numbers.

Comment

Chevron argued, with respect to the treatment related increase in duodenum tumors in mice shown by the NCI (1977) and interim report of the Chevron 1981 mouse study, that:

(a) Massive doses create grossly artificial conditions in the duodenum which are not representative of those which would occur under the most severe use conditions.

(b) There are no adverse systemic effects related to captan even at the massive doses tested. In fact, liver and lung tumors are decreased in male mice while survival is excellent.

(c) Evaluation of the risk to human health using ultra-conservative techniques indicates that there is negligible risk from exposure to captan even when worst case exposures are assumed.

(d) Using the same techniques for risk estimation, a greater risk can actually be demonstrated for pesticides which have no apparent oncogenic activity in toxicology studies in animals. Two hypothetical examples for which no tumors were detected in a lifetime study were analyzed. The upper 95 percent confidence limits on risk were calculated to be in the 10^{-4} to 10^{-6} range.

Response

The Agency feels that comment (a) is no longer relevant to the Agency's position because the risk assessment now presented is based upon a study done at lower doses than those discussed in this rebuttal comment.

Comment (b) is irrelevant to a risk assessment for duodenal tumors. Oncogenic compounds frequently produce tumors at one site or a few sites only without producing tumors in the

lung or liver. Adverse systemic effects and decreased survival are not related to or necessary for a finding of oncogenicity.

With respect to comment (c), the Agency does not consider the Chevron risk assessment to be "ultra conservative" because:

1) Chevron used only its own market basket survey data to estimate average residues. The Agency computed a somewhat higher residue (11.0 ug/day vs. Chevron's 6.8 ug/day) using several other sources in addition to Chevron's survey (see the Agency's exposure assessment).

2) Chevron used its survey to estimate maximum residues, but the sample size in that survey is too limited for such use. The Agency used the theoretical maximum residue contribution to the diet (TMRC) to estimate maximums.

3) Chevron apparently did not use a surface-area correction in extrapolation from mice to humans. The surface area adjustment is more conservative than the unadjusted weight basis apparently used by Chevron.

The Chevron risk assessment used both the one-hit and Mantel Bryan models for low dose extrapolation. It applied them to both the NCI (1977) and the Chevron mouse study (1981). Although the method of extrapolating from mice to humans is not specified it appears to have been done on an unadjusted weight basis.

The Agency did not use the one-hit or the Mantel Bryan models. The Agency used the linearized multistage model. It usually gives results closely similar to the one-hit model. The Mantel-Bryan model has an arbitrary slope. Furthermore, when applied to the two Chevron mouse studies (low dose and high dose) the results from the logprobit are unstable.

Finally, the Agency has used the surface area correction for extrapolation from mice to humans, while Chevron apparently did not.

Where the Agency and the Chevron risk assessments are most comparable (using a linear extrapolation, average dietary exposure, and the Chevron, 1981 study) Chevron's risk estimates were approximately an order of magnitude lower than the estimate by the Agency. The difference is likely to be mainly due to the difference in extrapolating from humans to animals, but this cannot be confirmed from the information available.

Chevron's argument that the risks are acceptable (comment (d)) is poorly based. Captan is being regulated under FIFRA which specifies that risks and benefits are to be balanced in reaching a decision on any pesticide. The examples given by Chevron of risks are mostly non-pesticidal (not regulated by FIFRA).

Furthermore, Chevron's argument does not take benefits into account. The statement by Chevron that the Agency's nitrosamine policy indicates a 10^{-6} risk to be acceptable is false. The nitrosamine policy uses the risk estimate based on a worst case assumption that untested nitrosamines are as potent as diethylnitrosamine to set priorities for review and data requirements. This policy does not indicate any blanket acceptance of a 10^{-6} risk.

The Chevron argument regarding upper limits on risk for compounds without positive oncogenic data is inappropriate to the captan decision. The Agency is aware that studies without positive effects do not provide a guarantee of zero risk. This in itself should not prevent the consideration of risk from exposure to a compound for which there are positive oncogenic data.

Since the risk assessment technique uses statistical upper confidence bounds, it is possible to compute upper limits on risk even when no tumors are observed in the long-term study. In such cases, the upper limit on risk will depend on how close the estimated human exposure is to the doses in the animal study (or to the highest dose tested if there are multiple doses). The closer the human exposure is to the animal dose, the higher the upper limit on the risk will be. One of Chevron's hypothetical examples assumed human exposures remarkably close to the animal dose. The example therefore produced high upper limits on risk (in the 10^{-4} range). Such high human exposure, relative to high doses in long term studies, is not typical of captan or most other pesticides.

2) Rebuttals by Stauffer Chemical Company

Comment

Stauffer commented that the Agency should not rely on the Innes, et. al. study (1969) results in mice to evaluate the oncogenic risks of captan.

Response

The Agency has not relied on the Innes, et. al. study for the PD 2/3. Instead, it has used the two Chevron studies in mice (Chevron, 1981 and Bio/Dynamics, 1983) and the Stauffer/ Chevron study in rats (1982) for the quantitative risk assessment.

Comment

Stauffer argues that the results at the very high doses in the NCI (1977) and the Chevron (1981) mouse studies do not provide a valid scientific basis for predicting that captan is an oncogenic hazard in man.

Response

The Agency now has the new Bio/Dynamics study (1983) in mice conducted at lower levels and has used it in the quantitative risk assessment. Although it can always be argued that an effect may not appear at lower levels than those tested, the available evidence for captan indicates that the tumor effect occurs at a wide range of dose levels.

Comment

Stauffer argued that the rodent models may be inappropriate for assessing human oncogenic risks of captan because human cells are more proficient in error-free excision repair.

Response

The Agency realizes that there are many uncertainties inherent in extrapolating from rodent studies to humans. The possible differences in DNA repair is just one of these factors. It is also possible that humans could be more susceptible than rodents to a chemical due to metabolic differences. There is not enough quantitative information on these effects to incorporate them in a risk assessment model.

Comment

Stauffer argues that the negative results in rats tested at doses equivalent to the mice doses (NCI 1977) indicate that larger mammals (such as humans) will be less sensitive to captan oncogenicity than mice.

Response

Since the Agency now has some evidence of oncogenicity in rats (Stauffer/Chevron rat study, 1982), the basis for this argument has disappeared. Stauffer commented that the age-adjusted mortality rates from malignant neoplasms appear to be stable in the United States since 1960, therefore, no increase from captan was seen.

The Agency feels that since oncogens frequently produce results in different organs for different species, this analysis does not provide evidence against the human oncogenicity of captan.

Comment

Stauffer presented a risk assessment using the one-hit model. The risks estimated for average dietary exposure were approximately one order of magnitude lower than those estimated by the Agency.

Response

The Agency has studied the Stauffer risk assessment. Since the dietary exposure estimates differed only slightly, the difference must be due to some difference in extrapolation procedures, probably from differences in the extrapolation from mice to humans. The Agency used the surface area correction, while Stauffer apparently did not.

Comment

Stauffer recommended that the Agency use a Carcinogenic Activity Indicator (CAI), based upon the tumor incidence and dose levels in the animal studies, as a factor in assessing oncogenic risk.

Response

The Agency has included the information contained in the CAI in the quantitative risk assessment.

3) Evaluation of Oncogenicity Studies by Dr. Melvin Reuber

Dr. Reuber submitted a paper, "The Carcinogenicity of Captan, September 4, 1980." He stated that he examined the histological sections and reevaluated the NCI rat and mouse studies (1977). He also reviewed the Innes et al. oral and subcutaneous mouse studies (1969).

Comment

Dr. Reuber's review of the NCI mouse experiment pointed out the existence of duodenal tumors in both male and female mice.

Response

The Agency has also stated its concern for these tumors. Two mouse studies (Chevron, 1981; Bio/Dynamics, 1983), completed since Dr. Reuber's report, were sponsored by Chevron Chemical Company. The studies demonstrated a higher incidence of these rare tumors and the Agency based its risk assessment on these two later studies.

Comment

Dr. Reuber stated that studies by Hazleton Laboratories in rats (1956), Industrial Bio-Test Laboratories in rats and mice, (IBT B9271,IBT B9267) and the Innes, et al. (1969) subcutaneous mouse studies were not satisfactory. He also noted that the Innes, et al. oral mouse study used low doses and that "mice in this study were examined particularly for tumors of the liver, lung, and lymphoreticular system, and the duodenum may not have been adequately examined."

Response

The Agency agrees. These studies are not suitable for risk assessment. The IBT studies were judged invalid by a joint US/Canadian governmental audit in 1979.

Comment

Dr. Reuber reported that his reexamination of the histology sections of the NCI rat study revealed many more neoplasms at all sites in both males and females than were originally reported by the NCI pathologists. He included summary tables which listed percentages of neoplasms in various organs.

Response

The Agency is not able to evaluate Dr. Reuber's report since he submitted only summary tables and did not evaluate the histology sections animal by animal as is normally required for a histopathology report. Without a report for each animal the Agency is not able to refer to the original slide to verify his conclusions. Stauffer sponsored a reevaluation of the tissues in question by William Carlton, DVM, Ph.D. Professor, Veterinary Pathology, School of Veterinary Pathology, Purdue University, Indiana. Dr. Carlton furnished an animal by animal report in which he found slightly different numbers of neoplasms than reported by the NCI pathologists (Carlton, 1981). Dr. Carlton concluded that "More neoplasms were diagnosed by us in the adrenal glands, mammary gland, pituitary gland and thyroid than reported in the NCI bioassay. These differences in numbers of neoplasms were due to the greater numbers of adenomas in our evaluation which lesions were generally designated hyperplasias in the NCI report. Such differences between histopathologic evaluations of a lesion as a hyperplasia or an adenoma are often met with and reflect variation in the criteria used by pathologists to differentiate between hyperplasia and adenoma. So long as the criteria for differentiation are uniformly applied across the experimental groups, the results obtained, while numerically different, generally lead to the same biological interpretation, such as was found in this case."

In any event, the Agency is not using this study in its quantitative risk assessment, rather a more recent study that shows more conclusive oncogenicity in the rat (Stauffer/Chevron, 1982).

b. Mutagenicity

1) Mutagenicity Rebuttal by Chevron Chemical Company

Chevron Chemical Company submitted extensive comments on the mutagenicity of captan. These are summarized and responded to in the following paragraphs.

Comment

Chevron stated that microbial and in vitro cell tests should not be used for risk assessment. Microbial testing does not reflect the actual results in vivo since captan is rapidly detoxified in mammalian tissue homogenates, blood, plasma, or by other thiol sources. Several sources were cited to support the inadequacy of microbial and in vitro cell culture testing for assessing mutagenic risk to humans. All in vivo studies except for the T.F.X. Collins dominant lethal study are negative. Attempts to duplicate the Collins dominant lethal study have produced negative results. Ample data exist to assess the mutagenic safety of captan. "The lack of mutagenicity in vivo in a vast array of studies, coupled with the fact that low toxicity permits testing a relatively high dose, clearly establish the safety of captan."

Response

The Agency has concluded that the risk of heritable mutagenic events in mammals appears to be either negligible or lower than can be detected in order to perform a risk assessment. However, somatic mutational events may occur in vivo since tumors are induced (or possibly promoted) in both the mouse and rat, although we cannot be sure of the mechanism.

Comment

Chevron stated that the evidence that captan has caused mutagenic effects in mammalian cells in vitro is weak and no reliance can be placed on it.

Response

The Agency agrees that some of the studies with positive results were not well reported, or used unusual cell lines or protocols; however, at least one of the studies (Tezuka et al. 1980) showed unquestionably positive results for chromosome aberrations and sister chromatid exchanges in Chinese hamster V79 cells.

Comment

Chevron mentioned that the major metabolite, tetrahydrophthalimide (THPI), is not mutagenic. They stated several times that the animal metabolites of captan are not mutagenic.

Response

The Agency is not aware of a battery of tests on THPI or other animal metabolites that would support this statement. No references are cited. (There is no need for testing the metabolites

in screening tests since they are present in the whole animal tests.)

Comment

Chevron presented many reasons why the microbial tests are "invalid" or "not meaningful." These reasons were generally concerned with the differences in metabolism, DNA repair, and cytology.

Response

The Agency does not agree that microbial evidence is "invalid" or "not meaningful." As Chevron pointed out, these tests are intended as screening tests and the Agency feels that they are valid and meaningful to establish the intrinsic mutagenicity of a test substance, e.g., the ability of a test substance to affect DNA.

Comment

Chevron cited several microbial studies (Ficson et al., 1977; Marshall et al., 1976; Simmon, 1977; Moriya et al., 1978; and Gabridge and Legator, 1969) to support the statement that the activity of captan is "eliminated" when systems which simulate the metabolic processes of whole animals are included. The metabolic systems include: rat liver S-9 microsomal mixture (with and without activating cofactors), rat or human blood, rat plasma, cysteine, or host mediated systems. The one host mediated study that reported positive results (Buselmaier, 1972) injected both the captan and the bacterial cells intraperitoneally which potentially exposed the bacteria directly to the unmetabolized captan. The preferred method exposes the intraperitoneal bacteria to the metabolites of the test substance administered by a different route.

Response

The Agency has referenced these studies in the PD 1 and generally agrees with the conclusions made by Chevron. It is not correct to say that the mutagenicity is "eliminated" by these systems because in many cases the activity is just reduced. A more accurate conclusion would be that the mutagenic activity of captan is reduced by these systems (and in some cases the assays are not able to detect any activity after inclusion of these systems). The Agency agrees that the apparent discrepancy of the positive results of the Buselmaier study may be explained by the above reason.

Comment

Chevron stated that captan is not mutagenic in mammalian cells in culture unless there was no liver metabolic system, or the serum normally included in the medium was deleted.

Response

The Agency realizes that the DNA damage induced in V-79 cells by captan was not detected after inclusion of rat liver S9 metabolic mixture (Swenberg et al. 1976), but DNA damage was detected in an unscheduled DNA synthesis assay (UDS) with and without rat liver microsomal mixture in SV-40 transformed human fibroblast VA 4 cells in culture (Ahmed et al., 1977). Although Arlett et al. (1975) reported that it was necessary to delete the serum from the culture medium in order to see mutation induction by captan at the ouabain locus in V-79 cells, Tezuka et al. (1980) reported both chromosome aberrations and sister chromatid exchanges with captan in V-79 cells with 10% fetal bovine serum added to the growth medium.

Comment

Chevron believes that the UDS study by Ahmed et al. (1977) is invalid because quantitative data were not reported for captan and no positive or negative control data were presented.

Response

The Agency acknowledges that the captan was reported merely as "+"; however, the authors stated this indicated a significant difference from the control at $P< 0.05$, using a subprogram t-test comparing the mean number of grains in controls and cells treated with pesticides at 95% confidence limits. The paper was otherwise well reported and the Agency believes that it is adequate for mutagenicity screening purposes since this type of DNA repair test is not used for risk assessment; therefore, exact quantification is not necessary.

Comment

Chevron feels that the cytogenetic assay by Legator et al. (1969) is not valid since the karyotype stability of the L-132 human embryonic lung and rat kangaroo cell lines was not stated, toxic levels of captan were used, the scoring methods were not described, the data were sparsely reported, the observed preferential breaking of the X chromosome in the rat kangaroo cells is unique to that cell line and cannot be predictive of effects on other cell lines, and no mammalian activation system was used.

Response

The Agency realizes that these cell lines are not often used for these purposes and that the study was not completely reported. The effect seen in rat kangaroo cells may be unique but that does not preclude the relevance of the underlying mutagenic response. Although toxic levels may have been used, the production of chromosome breaks is meaningful regardless of the mechanism involved. Despite these deficiencies, this study is useful to supplement the other information on production of chromosome

aberrations without metabolic activation. The results reported here are not unexpected in view of the positive findings of Tezuka et al. (1980).

Comment

Chevron stated that the in vitro cytogenetic study by Tezuka et al. (1978) in human fetal fibroblasts was negative. The PD 1 stated that the scoring methods were not described and that the usefulness of the study was therefore limited. Chevron feels that "Tezuka clearly described the scoring method used", and that mitosis was inhibited only at the higher doses of captan, rather than at all doses as stated in the Position Document.

Response

The Agency agrees that Tezuka et al. referenced Cohen and Hirschhorn in Chemical Mutagens, Vol 2 (ed.) A. Hollaender, Plenum, N.Y. 1971 for a description of their scoring methods; however, Cohen and Hirschhorn stated that "Each observer must establish and state his own criteria for scoring." Chevron is correct that captan did not inhibit mitosis at all doses. Of four doses with 4 hour treatment time, captan inhibited mitosis at the lowest and at the two high doses. Of four doses with 24 hour treatment time, captan inhibited mitosis at the three highest doses. The validity of this study is not particularly significant to the overall picture since there are adequate in vitro cytogenetic studies reporting chromosome aberrations, especially a later study performed by Tezuka et al. (1980) in a different cell line, which established that captan is able to cause chromosome aberrations in mammalian cells in culture under some conditions.

Comment

Chevron states that captan is rapidly and completely detoxified in animals. A number of metabolism studies are cited. (These studies are reported in the metabolism section of this document.) They say that "as a result of this unique detoxification, undegraded captan could not reach the gonads to induce a heritable mutation."

Response

The Agency agrees that the metabolism experiments (as reported in the metabolism section) indicate that it is unlikely that a significant amount of captan could reach the gonads. However, Chevron may be overstating the situation. The metabolism experiments show that captan is metabolized but not necessarily completely detoxified for the endpoint of concern (mutagenicity). The microbial experiments, particularly Moriya et al. (1978) in which preincubation of captan with S9 mixture, S9 fraction without cofactors necessary for activation of the microsomal enzymes, rat blood, or cysteine greatly reduced or eliminated the ability of captan to induce reverse mutations in Escherichia

coli WP2 hcr and Salmonella typhimurium, lend support to this theory; however, there is no quantitative study that provided definitive proof. It would be very difficult to devise such a study. It is theoretically possible that a very small amount of captan or an active metabolite reaching the gonads could cause a heritable mutation. Indeed, the Stauffer/Chevron 1982 rat study showed that captan can induce kidney tumors which indicates that an active form of captan can be found outside of the intestinal tract. The Agency prefers to have direct mammalian mutagenic studies as an indication of heritable events.

Comment

Chevron states that captan is not mutagenic in animal tests for somatic or heritable chromosomal aberrations. They cite the studies as reported in the Position Document 1. There are several dominant lethal studies, all reported as negative except for the studies performed by T.F.X. Collins (1972a). Chevron finds the following faults with this study: (1) No dose response was observed; doubling the dose did not result in a marked increase in the effect. At doses where the effect is nowhere near the maximum (i.e., only a small percentage of animals effected), large increases in dose should cause a significant increase in effect, which does not happen in the Collins study. For example, the mean number of early fetal deaths per pregnancy reported during week 4 of mating for rats given 100 mg/kg/day captan by gavage is reported as 1.00 and is statistically different from control. However, when the dose is doubled, the index is only 1.07 and due to the large variance it is not statistically significant. (2) The administering of captan by gavage was not appropriate since high local concentrations of captan could overwhelm the normal detoxification mechanism in the gastrointestinal tract. Intragastric administration is abnormal for a compound which is ingested with the diet and degraded and "detoxified" within the gastrointestinal tract. The dietary route would have been more appropriate for evaluating the mutagenic potential of captan. (3) The raw data is no longer available and validation of the study is not possible. A reproduction study by Collins (1972b) did not reveal any dominant lethal effect as measured by a decrease in litter size; therefore, his own data is in conflict. Other similar dominant lethal studies are negative (Epstein et al., 1972; Simmon et al., 1977; and Tezuka et al., 1978)

Response

The Agency agrees that all other animal studies are negative. In the Collins study (1972a), dosing by gavage is not objectionable; a high dose is desirable for a screening study. However, this dominant lethal study would not be suitable for risk assessment. In addition, the effects did not occur at a consistent spermatogenesis stage. The results are not found in other similar studies. It unfortunately is not possible to have much confidence in the results of this study since the raw data are not available for reevaluation and similar studies are negative.

In any event, the definitive study performed for risk assessment, the SRI 1977 heritable translocation mouse study, was found to be negative by an EPA sponsored Gene-Tox committee (Generoso et al. 1980).

Comment

Chevron submitted a mouse color coat spot somatic cell assay (Litton Bionetics, 1980) which was negative. "This test is uniquely sensitive for an *in vivo* mammalian assay since a large number of potentially mutable loci are evaluated....The sensitivity of the captan study was further augmented by nearly doubling the group size to 105 and extending the treatment period to the 5 day interval, days 8 to 12 of pregnancy."

Response

The Agency concurs that this study was negative. This study is further described in the mutagenicity risk assessment section of this document.

Comment

Chevron stated that captan produced negative results in three Drosophila assays.

Response

The Agency is not able to place much reliance on negative Drosophila tests in risk assessment since there may be differences in insect metabolism and intake of the test substance as compared to mammalian systems.

2) Mutagenicity Rebuttal by Stauffer Chemical Company

Stauffer Chemical Company submitted many comments on the mutagenicity of captan, many of which are similar to the comments by Chevron Chemical Company. The following section summarizes and responds to the comments unique to the Stauffer submission.

Comment

In general, Stauffer maintains that bacterial, yeast, fungal, and mammalian cells *in vitro* systems are not relevant for predicting mutagenic risk to humans.

Response

The Agency agrees. The risk assessment of captan in this document is primarily based on *in vivo* studies.

Comment

Stauffer points out that unscheduled DNA synthesis (UDS) assays measures only DNA repair and that the only conclusions

that the Agency should draw are that the cells may have an excision repair process for repairing captan induced modifications in cellular DNA and that the existence of this repair process is a mitigating factor in determining risk.

Response

The Agency agrees that DNA repair assays are not particularly useful in determining risk. They are primarily used as a relatively inexpensive screening study to determine if a test substance can affect DNA. Heritable risk assessment testing must involve an *in vivo* test in mammals with intact DNA repair systems measuring gonadal mutations, alkylations, or similar process depending on the mechanism of action of the mutagen.

Comment

Stauffer stated that the dose was very high in the V-79 cells in culture assay by Arlett et al. (1975) and that an UDS assay in WI-38 culture human fibroblast was determined to be negative (after a repeat experiment; the first experiment showed that captan appeared to induce UDS after metabolic activation) (Simmon et al. 1977).

Response

The Agency does not use the V-79 gene mutation assay for risk assessment, therefore the dose is irrelevant. The assay merely shows the potential for intrinsic mutagenic activity. A negative UDS assay is not incompatable with a positive gene mutation assay and does not mitigate the necessity to perform *in vivo* tests.

Comment

Stauffer submitted a letter from Dr. Shirasu responding to the PD 1 comment that the scoring criteria for cells in a chromosome analysis (Tezuka, Ando, Suzuki, Terahata, Moriya and Shirasu, 1978) was not described. In the letter Dr. Shirasu states that well spread metaphases with 45 or 46 centromeres (2n=46) were observed.

Response

The Agency notes that the scoring criteria has not yet been described. This illustrates the difficulty of fully analyzing studies published in the literature. Detailed documentation is needed, especially to accept a study reporting negative results. In this case, judging from the positive results reported for mitomycin C and the positive results seen for captan in the same laboratory in V-79 cells in culture (Tezuka et al. 1980) the study is probably adequately performed. The Agency still is not sure what kinds of chromosome aberrations were included in the analysis, and more important, what kinds, if any, were excluded.

Comment

Stauffer described a study by Fry and Ficsor in which 50% captan was administered at 250 mg/kg by i.p. injection to Upjohn Swiss albino mice. The numbers and handling of the mice were not well described. Metaphase spreads were counted for chromosome aberrations from animals sacrificed at 6, 12, 30, and 54 hours after treatment. Stauffer states that captan "did not cause any statistically significant increase in chromosome aberrations in treated animals relative to controls."

Response

The Agency was not able to fully analyze this study from the abbreviated information provided in the report (published as a "Short Communication" rather than a full paper). The authors themselves state that "Because of these unique chromosome rearrangements," (3 metacentric chromosomes) "it cannot be stated with certainty that 250 mg captan/kg i.p. does not break chromosomes in vivo."

Comment

Stauffer supports the mouse dominant lethal study performed by Tezuka et al. (1978) with a letter from Dr. Shirasu (one of the authors) in which he responds to the PD 1 criticisms. The PD1 stated that the application of the formula given in the paper for calculation of the percentage of dominant-lethal mutations yielded results that differ from those reported. Dr. Shirasu stated that this "formula was mistaken for the following; (1 - live embryos per implants in experiment/live embryos per implants in control) x 100. This calculation is appropriate for for the estimation of weak mutagen as proposed by Rohrborn (Vogel and Rohrborn, 1970). If captan causes dominant lethal mutations, a significant increase in the post-implantation losses, which is direct evidence for dominant lethals, will be observed. However, our results showed no such increase even in the 600 mg/kg/day group." The PD 1 also objected to the protocol in that females were caged with males for 2 to 4 day intervals, depending on whether a plug was observed, the more active males would contribute more females to the experiment. Dr. Shirasu elaborated on this point, stating that the mating was controlled to obtain a maximum of 2 copulated female per week (to prevent a low sperm count of males). Stauffer commented that the PD 1 criticism of the 6 week mating period was unwarranted since, if Collins' experiments are correct, then all spermatogenic stages appear to be affected by captan except the spermatogonial stages that would appear during the 6th week of mating. Therefore, 6 weeks constitutes an ample sampling period.

Response

The Agency has concluded that the above information from Dr. Shirasu and the comparison by Stauffer with the Collins'

study (Collins, 1972a) is adequate to allow this study to be accepted as evidence that captan does not produce dominant lethality under the conditions of this study at oral doses of captan up to 600 mg/kg for 5 days. The Agency withdraws its objections to the use of this study.

Comment

Stauffer cautions that quantitative risk assessments should not be attempted from assays using microbial cells or mammalian cells in culture due to differences in DNA repair. Extensive references are cited to document this. In addition, they point out that there are DNA repair differences between hamster and human cells in culture as evidenced by differences to the mutagenic action of caffeine. They state that "The Agency should consider the differences in DNA repair mechanisms in extrapolating mutagenicity studies in mice to humans to estimate mutagenic risk potential....risk estimates for humans should be decreased when extrapolating from rodents to humans."

Response

The Agency is not considering performing quantitative risk assessments from assays using cells in culture. At this time the Agency is not quantitatively extrapolating mutagenic risk from rodents to humans in the case of captan. In any event, DNA repair differences between rodents and humans would be difficult to quantitate.

c. Teratogenicity and Fetotoxicity

Comment

Stauffer Chemical Company cited studies that have been reviewed in the teratogenic risk section of this document and stated that they concurred with the Agency's finding (in the PD 1) that all currently available data on potential teratogenic and fetotoxic effects of captan are insufficient to raise a presumption under 40 CFR 162.11 (a)(3)(ii)(B). They quote a review of the literature by their consultant, William J. Scott, D.V.M., Ph.D., Associate Professor of Research Pediatrics, Children's Hospital Medical Center, Cincinnati, Ohio, that "captan represents very little hazard as a human teratogen." He recommended additional testing before any final assessment of captan's potential teratogenicity.

Response

The Agency has not found significant teratogenic risk at this time; however, an additional test has been required to clarify some unusual findings in one of the older experiments (Robens, 1970).

d. Metabolism

Stauffer Chemical Company presented a review of the metabolism and an argument for the detoxification of captan in vivo. The Agency has reviewed this literature separately in this document; however, the Stauffer rebuttal is summarized here.

Comment

Stauffer suggested that thiophosgene is directly responsible for initiating induction of tumors of the upper small intestine in mice in the NCI (1977) and Chevron/Stauffer (1982) studies.

Response

The Agency agrees that this appears to be the case.

Comment

Stauffer concluded that captan is detoxified in the gastrointestinal tract. "There is strong evidence that mammals can detoxify captan and that captan and its metabolites do not persist in the body." "One study" (DeBaun et al. 1974) "of the metabolism of captan suggests that the detoxification process is saturable. If it is saturable, test animals are disproportionately vulnerable to large doses. There is no evidence to show that ingestion of small amounts of captan residue presents a risk to health."

Stauffer pointed out that the duodenal tumors as seen in the NCI mouse assay (1977) might be explained by "the relatively alkaline nature of this region of the gut and the fact that captan is more susceptible to hydrolytic cleavage at alkaline pH (Daines, et al. 1957). Hydrolysis under these conditions and reaction with duodenal thiols may account in part for the release of thiophosgene at this location, alkylation of macromolecules including DNA, and subsequent tumor formation. The relevance and significance of tumor induction under these massive dosing conditions must be seriously examined and questioned by the Agency in assessing human risk based on the NCI study." Stauffer also stated that "Because exposure of the general population to captan is through ingestion and because a detoxification process exists in the gastrointestinal tract, studies which use i.p. injections or otherwise bypass the gastrointestinal tract are unrealistic for predicting human risks from exposure to captan."

Response

The Agency considers this argument to be well presented and may have some validity; however, there are some problems with it. The relevant metabolic data have generally been derived from rat studies. No gastrointestional tumors have been found in the rat, thus metabolism from a species that does not produce

these tumors (and yet thiophosgene was formed) is being used to explain the formation of the tumors in mice (for which no metabolic data exists). Quantitative metabolic data in the mouse must be presented to support this argument. The Agency will not require these data since a risk assessment has been performed without considering any possible detoxification of

captan. It also might be noted that the rat study (which had not been completed at the time of this rebuttal by Stauffer) has shown kidney tumors at lower levels of captan than used in the NCI and Chevron high dose mouse experiment.

Since Stauffer's rebuttal was presented, a low dose mouse experiment (Bio/Dynamics, 1983) has also been completed and submitted to the Agency. It also shows these normally rare intestinal tumors at a level of dose similar to that of the Chevron high dose mouse study. This shows that if there is an detoxification effect on captan, it occurs at levels less than 100 ppm in the diet. This level is much closer to actual captan dietary residue levels. In the mouse, 100 ppm is roughly equivalent to 15 mg/kg of captan. For a dietary exposure using the theoretical maximum contribution to the diet of 7.013 mg captan in an average 1.5 kg diet per day, a 60 kg man would receive 0.117 mg/kg. This potential exposure is only two orders of magnitude under the lowest tested dose.

In the absence of quantitative data on a detoxification mechanism for captan and considering the presence of tumors at low levels in the mouse and rat, the Agency has concluded that it can not justify including this inactivation theory in its oncogenic risk assessment.

Comment

Stauffer pointed out that mammalian DNA repair may lessen the oncogenic risk. "Even if an organism is unable to detoxify by biochemical reactions all of the captan to which it has been exposed, the organism may have other lines of defense against tumor formation. If captan causes tumor development by reacting (directly or indirectly) with cellular DNA, the cell may be able to repair the altered DNA, reversing the initial step in tumor formation. Thus, all relevant mutagenic test activity should be considered by EPA in explaining the mechanism by which captan produces intestinal tumors in mice at high doses, and in extrapolating these findings to an assessment of human risk. "

Response

The Agency believes that any effect of DNA repair in decreasing the possibility of somatic mutations which might induce tumors would be accounted for by observing actual tumor induction in the rodents. In addition, any difference in rodent and human DNA repair is theoretical and cannot be incorporated into a risk assessment model at this time.

e. Ecological Effects

According to the Stauffer Chemical Company's rebuttal of November 26, 1980 to the Agency's notice of RPAR based on aquatic risk, they are "unaware of any aquatic use recommendations on captan labels registered by the Agency." Stauffer's rebuttal of the aquatic risk criterion for captan is accepted (Stevens, 1981). Although captan is highly toxic to fish (not moderately so as stated in the rebuttal) and under 40 CFR 162.11 (a)(3)(i)(B)(3) it would appear, on the surface, that the criterion had been met, there are several factors which the Agency must consider.

The risk criteria under 162.11 assume direct application to water. Since there are no registered aquatic uses, aquatic contamination could occur only indirectly, i.e., through drift, runoff or leaching. Additionally, the Agency at this time has no reliable estimate nor measured residue data to suggest that the magnitude of potential indirect aquatic contamination would be great enough to result in unreasonable adverse effects on nontarget aquatic species. Furthermore, captan hydrolyzes rapidly in water (half-life of 1 to 2 days, usually 1/2 day or less; Stauffer Ref. 139 and Wolf et al., Ref 140) and apparently can degrade rapidly in soil under appropriate environmental conditions, such as observed in model ecosystems. However, under certain field conditions captan residues may persist longer, perhaps up to 2-3 weeks. In specific locales, such as seed treatments, captan residues may persist longer than observed in model ecosystems, but these uses are not likely to result in unreasonable adverse effects to nontarget aquatic species because they have low rates of application.

The Agency agrees that the available data do not provide an adequate basis for a presumption based on aquatic risk. Any non-target species effects, if any, are likely to be localized and would not be expected to be unreasonable. However, any significant change in use or exposure data could change the Agency's position.

2. Exposure

The Agency received comments relating to exposure in response to the captan PD 1. Those rebuttals and Agency responses are contained in the following paragraphs.

In the PD 1, a theoretical worst-case dietary exposure of 0.117 mg of captan per kg of body weight per day was calculated. This calculation was based on existing tolerances, the extent of crop treated (if available) and assumed an average daily diet of 1.5 kg for a 60 kg person. The Agency acknowledged that actual levels of captan would probably be lower.

Stauffer Chemical Company and Chevron Chemical Company submitted data on commodities purchased from retail stores from across the country. They claimed that these data demonstrate that the Agency over-estimated the dietary exposure. The Agency

considered the FDA Market Basket Survey Data, FDA Compliance/ Surveillance Survey Data, and data submitted by Stauffer and Chevron and calculated the dietary exposure and potential risk using these data. However, the Agency will not use these data for regulatory purposes because: (1) the average residues may represent both treated and untreated samples; (2) there may be inconsistencies in field application practices; (3) the handling practices of the commodities by retailers may vary; and (4) not all crops were represented in these surveys. In addition, because tolerances represent the residues that could be legally present, the Agency has decided to base its dietary exposure and risk assessment on tolerances.

In PD 1, the Agency had very little data available in order to assess exposure to workers. Since the publication of the PD 1, the Agency has received new studies and has performed an updated exposure analysis for the PD 2/3.

The Environmental Fate Profile for the PD 1 is still applicable for the PD 2/3 (Saito, 1981)

3. Benefits

1,215 captan RPAR rebuttal statements were reviewed for information on benefits, use practices, and alternative controls. Among these, 1152 expressed endorsement of captan products and the essentiality of various agricultural uses of captan. Individuals expressed endorsements in terms of experience with captan products (e.g., crops treated, diseases controlled, lack of adverse health effects, and impact of cancellation). Many of these endorsements (504) were submitted through form letters. One of the form letters indicated that captan was not used, another stated that a substitute chemical could replace captan for a specific site. None of the endorsements contained information that could be useful for preparing use data reports for economic or exposure analyses or for assessment of alternatives.

Five rebuttals did not address positive benefits; two of these requested information on risks associated with use; one was a brief doctor's statement which claimed to be aware of a severe physical reaction due to captan exposure; and one called attention to the use of captan in shampoos. One respondent stated that cost benefits data "is not garnered from objective sources and is not critically assessed."

The remaining 58 rebuttals submitted by growers, agricultural chemical manufacturers and distributors, state extension service personnel, grower associations, pest control applicators, and seed treatment contained useful information which was considered in developing the benefits assessment in chapter III. The majority of these rebuttals address uses for seed treatment and fruit, two addressed forest tree and ornamental uses. Rebuttals on vegetable foliar uses were scant.

B. ADDITIONAL INFORMATION ON RISKS

1. Oncogenicity

Since the PD 1 on captan was published, additional information on oncogenicity has been submitted to the Agency. Chevron conducted a high-dose feeding study (Chevron, 1981) and a low-dose feeding study in mice (Chevron, 1983). Stauffer conducted a feeding study in rats (Stauffer, 1982). An analysis of the data from these three chronic feeding studies show a dose-tumor relationship with a weight of evidence classification of B 2 (probable human carcinogen) under the draft EPA guidelines (49 FR 46294). This conclusion is based on adenocarcinomas of the digestive tract in both sexes of the two cited mouse studies and on kidney tumors in male rats. This is further supported by evidence from short term studies that show that captan is an alkylator.

A detailed description of the above cited studies and the oncogenic risk analysis is presented in Section II.C. of this chapter.

2. Reproduction

The International Research and Development Corporation (IRDC) conducted a 3-generation reproduction study in COBS CD rats for the Chevron Chemical Company (1982). Rats were fed captan in the diet at doses of 25, 100, 250 and 500 mg/kg/day throughout the study. For each generation (parental, F_1 and F_2), 15 males were mated with 30 females. Treatment related effects attributable to the administration included reduced parenteral (male and female) weight gain at doses of 100, 250 and 500 mg/kg, reduced pup litter weights in all litters at all dosage levels, and reduced food consumption in all treatment groups at all dosage levels except for F_1 males (25 mg/kg) and F_2 females (25 and 120 mg/kg).

A one generation rat study, submitted by Chevron, was performed by IRDC (1982). Captan was administered in the diet at 0, 6, 12.5, and 25 mg/kg/day to 15 male and 30 female COBS rats per dose level. No treatment related effects due to captan were seen. This study is not adequate by itself but is sufficient when used to supplement the three generation rat study (IRDC #153-096, Jan. 7, 1982) to satisfy the reproduction testing requirements. When used in conjunction with the three generation rat study, the NOEL for toxic effects is 12.5 mg/kg/day and the LEL is 25 mg/kg/day.

3. Teratology/Fetotoxicity

Robens et al. (1970) reported captan to be toxic and teratogenic in the Golden Syrian hamster. Captan was administered orally to groups varying in size from 2 to 10 females on gestation days 6 to 10 at cumulation doses of 500, 1,000, 1,500 and 2,500 mg/kg, or single oral doses of 200,

300, 400, 500, 600, 750 and 1,500 mg/kg on day 7 and 8. Increased maternal mortality was observed at cumulative doses of 1,500 mg/kg or more and at single doses of 600 mg/kg or more. Fetal weight was reduced after the 2,500 mg/kg cumulative and the 1,000 mg/kg single doses. Terata were seen at the 2,500 mg/kg cumulative dose and at single doses of 300 mg/kg or more, and a dose-response trend was evident. The terata included exencephaly and fused ribs (the latter may be attributable to maternal stress). Although it is difficult to analyze the results reported in this study because of omissions and/or inconsistencies in tabular data and because statistical analyses were not performed, they nevertheless are suggestive for teratogenicity.

E. I. Goldenthal (1978) performed a study at International Research and Development Corp. for Chevron Chemical Corp. Captan doses of 50, 200, and 400 mg/kg/day were administered to Golden Syrian hamsters by gavage on day 5 through 10 of gestation. There were 30 mated females in each of the captan treatment and vehicle control groups. The results suggested that captan produced maternal deaths and weight loss at doses of 200 and 400 mg/kg and was also fetotoxic at the 400 mg/kg dose, resulting in decreases in the number of viable fetuses, male to female sex ratio and fetal weight, and increases in the number of early and late resorptions and postimplantation losses. In addition, rib anomalies (primarily bent ribs) were produced by the 400 mg/kg dose level. These anomalies may be accounted for by a maternal stress effect upon the fetus rather than to a teratogenic effect.

A preliminary screening study was performed for NCI by Bionetics Research Labs (1968). Captan at 100 mg/kg subcutaneously, or orally, was administered to 21 C57BL6 female mice on gestation days 6 to 14 and to 13 AKR female mice on gestation days 6 to 15. Following subcutaneous injection, captan was associated with maternal weight loss, increased fetal mortality, reduced fetuses per litter and reduced fetal weights in both strains of mice. An increased number of abnormal fetuses, largely resulting from the occurrence of microphthalmia, was reported in the C57BL6 strain but not in the AKR strain of mice. Following oral administration of captan, maternal weight loss occurred in mice without prominent signs of fetal toxicity or abnormalities.

Four female New Zealand White rabbits were dosed with 80 mg/kg captan by gastric intubation on days 7-12 of gestation and no maternal toxicity, fetotoxicity or teratogenicity was seen (Fabro et al. 1966). Only one dose level was tested and the number of animals tested was very small, so the negative results are less convincing.

A study in New Zealand White rabbits was conducted by the Chevron Chemical Company (1981, EPA Accession No. 246624). Captan was administered by intragastric intubation at doses of 6, 12, 25, and 60 mg/kg/day to groups of 15 female rabbits

on days 6 through 28 of gestation. The compound produced maternal weight loss at doses of 12, 25, and 60 mg/kg which was dose-related, and reduced litter weights and mean fetal weights at the 60 mg/kg dose level. No teratogenic effects were observed.

The following studies were evaluated and should not be used for regulatory purposes due to various inadequacies:

Two groups of 10 French Charles River Wistar rats were treated intraperitoneally with 25 mg/kg captan (Alnot et al. 1974). The dose level was excessively high since, of the 20 treated animals, 8 were dead 2-10 days after i.p. injection. Captan was found to be embryotoxic and cataracts were found among the surviving fetuses.

Earl et al. (1973) administered captan by capsule to beagle dogs throughout gestation at daily doses of 15, 30, or 60 mg/kg/day. There were 5 female dogs per group. The most prominent effects occurred at the 30 mg/kg dosage level and included increases in the number of pups and litters with terata, the number of litters with stillbirths, and percentage of pup stillborn. The observed terata at the 30 mg/kg dose level included crooked tails (2 pups) and gastroschisis (1 pup). Additional abnormalities seen at other dose levels included single kidney (1 pup at 15 mg/kg and 1 pup at 60 mg/kg) and hydrocephalus plus open fontanel (1 pup at 60 mg/kg). None of the abnormalities were present in control dogs. Since the effects were not dose related and showed no consistent pattern, the results are questionable.

A chick embryo study (Verrett et al., 1969) indicated that captan (6 mg/kg) and its metabolite tetrahydrophthalimide have teratogenic activity, but since the results are given as the total number of malformations seen at all dose levels, it is not possible to determine the magnitude of the effects at the individual dose levels. This study is useful as a screening study but is not relevant for mammalian risk.

Courtney et al. (1978) reported finding no teratogenic effects in CD1 mice at a dosage of 100 mg/kg orally and subcutaneously, and an inhalation dosage of 483 mg/m^3. Fetotoxicity was reported in mice treated subcutaneously. The report does not have sufficient data to evaluate. A monkey study was reported as negative (however, 3 abortions among 7 monkeys at the highest dosage could be a matter of concern).

The IBT studies (Kennedy et al. 1968; Kennedy et al. 1975; and Von Druska et al. 1971) have all been declared invalid by a Canadian/U.S. audit (1979).

The above teratology studies suggest that captan may have the capacity to produce fetal abnormalities in lab animals.

This was indicated by findings of fused and/or bent ribs (which may have resulted from maternal stress) and exencephaly in hamsters following the oral route of administration, and microphthalmia in mice following the intraperitoneal (but not the oral) route of administration. Several other low level abnormalities were seen in beagle dogs following oral administration, but no teratogenic effects were seen in studies in rabbits.

Because the results of the Robens et al. (1971) study with hamsters were suggestive for teratogenicity, the Agency has required an additional study in hamsters, dosing on only one day rather than repeated daily dosing as usually done. One set of hamsters should be administered a range of doses on day 7 of gestation, and another set should be treated on day 8 of gestation. This study will determine the no-observable-effect-level (NOEL).

4. Metabolism (Pharmacokinetics)

Pharmacokinetic studies were performed in rats with captan radioactively labeled either at a ring position (C^{14}) or on the trichloromethylthio side chain (C^{14} or S^{35}). Radiolabeled captan was administered by the oral or intraperitoneal routes in doses ranging from 6 to 650 mg/kg.

Captan undergoes rapid hydrolysis with scission of the N-S bond in blood and in the gut. At blood pH (alkaline) and in the presence of thiols, captan is hydrolyzed to THPI (tetrahydrophthalimide) and to a derivative of the trichloromethylthio group. In the gut there is evidence of rapid reaction with sulfite or thiosulfate radicals resulting in THPI and various products derived from the trichloromethylthio moiety. The gut hydrolysis is rapid and consistent with the fact that only trace amounts of unchanged captan are detected in rat feces after an oral dose of 650 mg/kg (DeBaun et al. 1974).

The metabolism of captan has been investigated almost exclusively in rats, although one distribution study has been conducted in mice (Selski, 1981). Since the molecule hydrolyzes into two different parts, the fate of the molecule has been followed by radiolabels in two different positions. To study the THPI part of the molecule, ^{14}C uniformly labeled in the carbonyl group was used (Hoffman et al. 1973); to study the trichloromethylthio moiety, the ^{14}C-label at the methyl carbon was used (DeBaun et al. 1974). In addition, some studies have attempted to follow the metabolism of captan labeled with ^{35}S in the trichloromethylthio moiety (Seidler et al. 1971; Couch et al. 1977).

The fate of captan uniformly labeled in the carbonyl group was elucidated by Hoffman et al. (1973). After oral administration of single oral doses of 77.4 to 91.9 mg/kg of $^{14}C{=}O$ captan, no unchanged captan was detected in the urine. Rats excreted 92% of the radiolabel within 48 hours and 96.8% of the radiolabel within

96 hours. Most of the ^{14}C (84.5%) was excreted in the urine with only 12.3% excreted in the feces and none detected in expired air. Tissue residues at 96 hours did not exceed 0.1% of the total ^{14}C administered. No significant difference in elimination rates of the ^{14}C was detected between male and female rats.

In vivo biotransformation of the ring structure of captan followed four pathways after initial hydrolytic cleavage of ^{14}C-captan to THPI and the trichloromethylthio side chain moiety (Figure 1). THPI was the precursor for these four pathways since identical urinary metabolites were found after oral administration of THPI-^{14}C=O. Of the ^{14}C that was found in rat urine 15% was present as ^{14}C-THPI.

The following metabolic pathways were observed (Figure 1):

a. Pathway (I): the major urinary metabolite was the trans-3-hydroxy product, 3-OH-THPI, which accounted for 38.4% of the urinary ^{14}C. This was further degraded to 3-OH-THPAM (trans-1-carboxy-2-carboxamido-3-hydroxy-4-cyclohexene), which represented 7.1% of the urinary ^{14}C.

b. Pathway (II): epoxidation of THPI in positions 4 and 5. In rat urine, 5.2% of the ^{14}C-THPI that was found was present as ^{14}C-THPI-epoxide (trans-1,2-dicarboximido-4,5-epoxy-cyclohexane). This compound was subsequently hydrolyzed to yield 4,5-di-OH-THPI (trans-1,2-dicarboximido-4,5-dihydroxy-cyclohexane), which represents 10.9% of the urinary ^{14}C. Intraperitoneal injection of THPI-epoxide to rats resulted mainly in unchanged epoxide and an unidentified "minor" metabolite.

c. Pathway (III): hydrolysis of THPI to yield 11.7% of THPAM (trans-1-carboxy-2-carboximido-4-cyclohexene).

d. Pathway (IV): ring hydroxylation of THPI in the 5 position and subsequent rearrangement of the double bond giving 5-OH-THPI (10.1%).

e. A minor pathway involving conversion of THPI to an unidentified metabolite which accounted for 1.2% of the urinary ^{14}C.

Neither glucuronide nor sulfate conjugates were detected in rat urine. Reaction of the urine with B-glucuronidase and sulfatase gave negative results. Since the molecular weight of the THPI derivatives were all below 325 and since no conjugation was detected, biliary excretion was considered unlikely. There was no attempt to analyze fecal metabolites. Tissue distribution studies revealed tissue residues (expressed as ppm captan equivalents) to range from 5.47 (in hide) to 42.90 (in kidney) at 24 hours. At 48 hours, the range of values was 0.0 to 2.83 ppm.

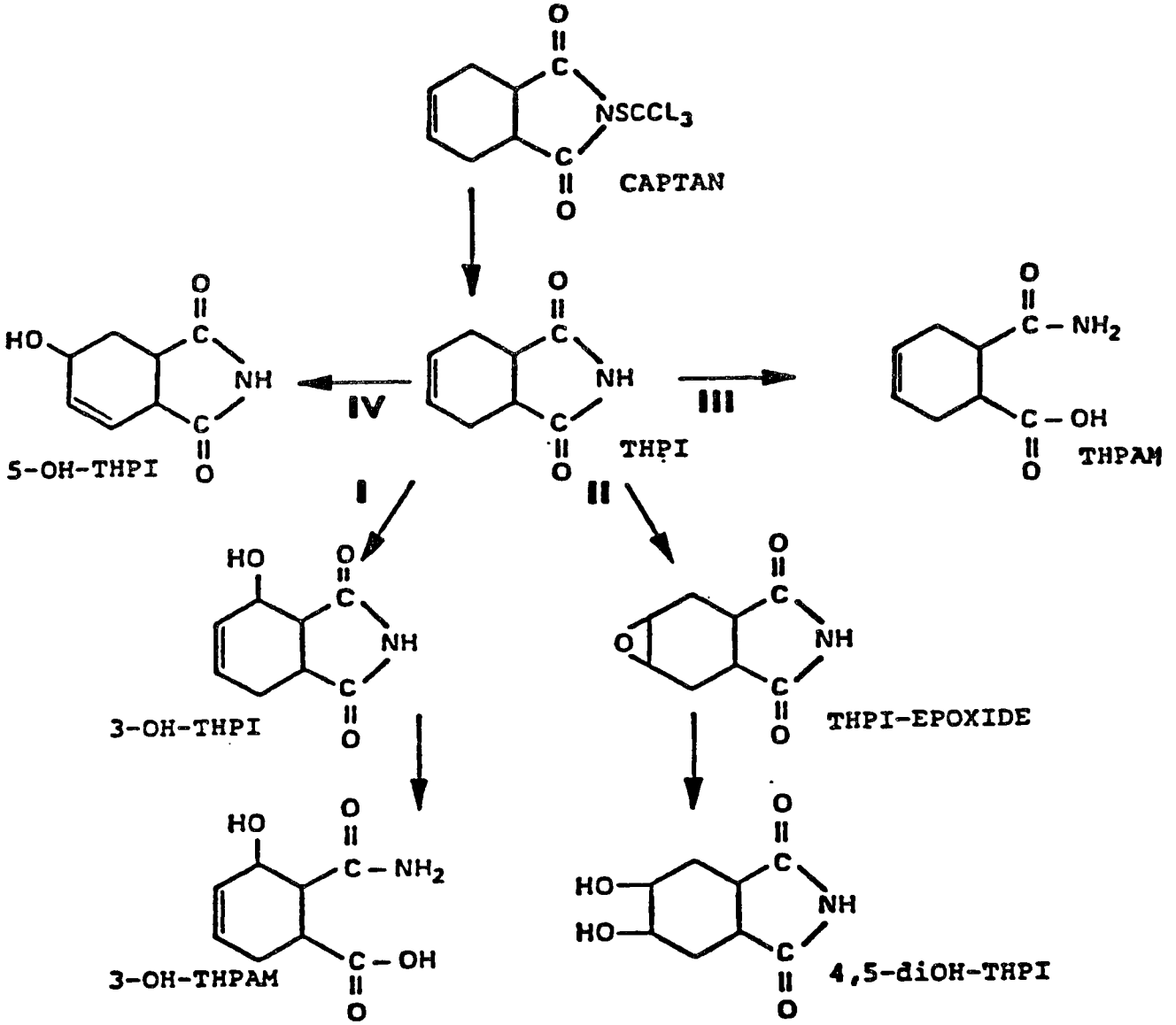


Figure 1. Urinary Metabolites of ^{14}C-Captan in the Rat

The values were negligible thereafter. No fat accumulation was noted.

The metabolic fate of captan labeled on the trichloromethylthio moiety was monitored after oral or intraperitoneal administration to rats (DeBaun et al., 1974). After a single oral dose of ^{14}C-captan (100 mg/kg), 50% of the ^{14}C was excreted in urine, feces, and air within 9 hours. In comparison, excretion of 50% of a single intraperitoneal dose of ^{14}C-captan did not occur until 48 hours after dosing. Four days after a single oral dose, the cumulative distribution of the ^{14}C was 51.8% in urine, 15.9% in feces, and 22.8% in expired air. Comparable figures for the intraperitoneal route after 4 days were 45.5% in urine, 5.8% in feces, and 18.4% in expired air; between 4 and 10 days, another 14.8% was eliminated in urine and 18.8% in feces.

In vivo biotransformation of the side chain moiety of orally administered captan followed three Pathways after initial hydrolytic cleavage of ^{14}C-captan to the THPI ring structure and the trichloromethylthio moiety (Figure 2).

a. Pathway I: an initial reaction involving the formation of thiophosgene from the trichloromethylthio side chain moiety. The thiophosgene is the precursor for the remaining pathways described below. Thiophosgene is probably formed in the more alkaline parts of the gut. In vivo, thiophosgene may arise from reaction of Na_2SO_3 or thiosulfates with captan. This reaction also occurs in vitro.

b. Pathway II: reaction of thiophosgene with sulfite ion to yield dithiobis (methanesulfonic acid) (metabolite A) and its disulfide monoxide derivative (metabolite B). The former metabolite represented 54% and the latter metabolite represented 13.8% of the urinary ^{14}C, respectively. These metabolites are the major ones formed after oral administration, but these are not formed after interperitoneal administration indicating that the reaction with sulfite ion takes place in the gut or by action of the intestinal mucosa.

c. Pathway III: condensation of thiophosgene with free cysteine or free glutathione to form a thiazolidine derivative, thiazolidine-2-thione-carboxylic acid (metabolite C), which is not metabolized further in the rat and is excreted in the urine. This metabolite represented 18.6% of the urinary ^{14}C.

d. Pathway IV: hydrolysis and/or oxidation of thiophosgene to CO_2.

Following oral administration of ^{14}C-captan, metabolites A, B and C accounted for 86% of the urinary radioactivity. After

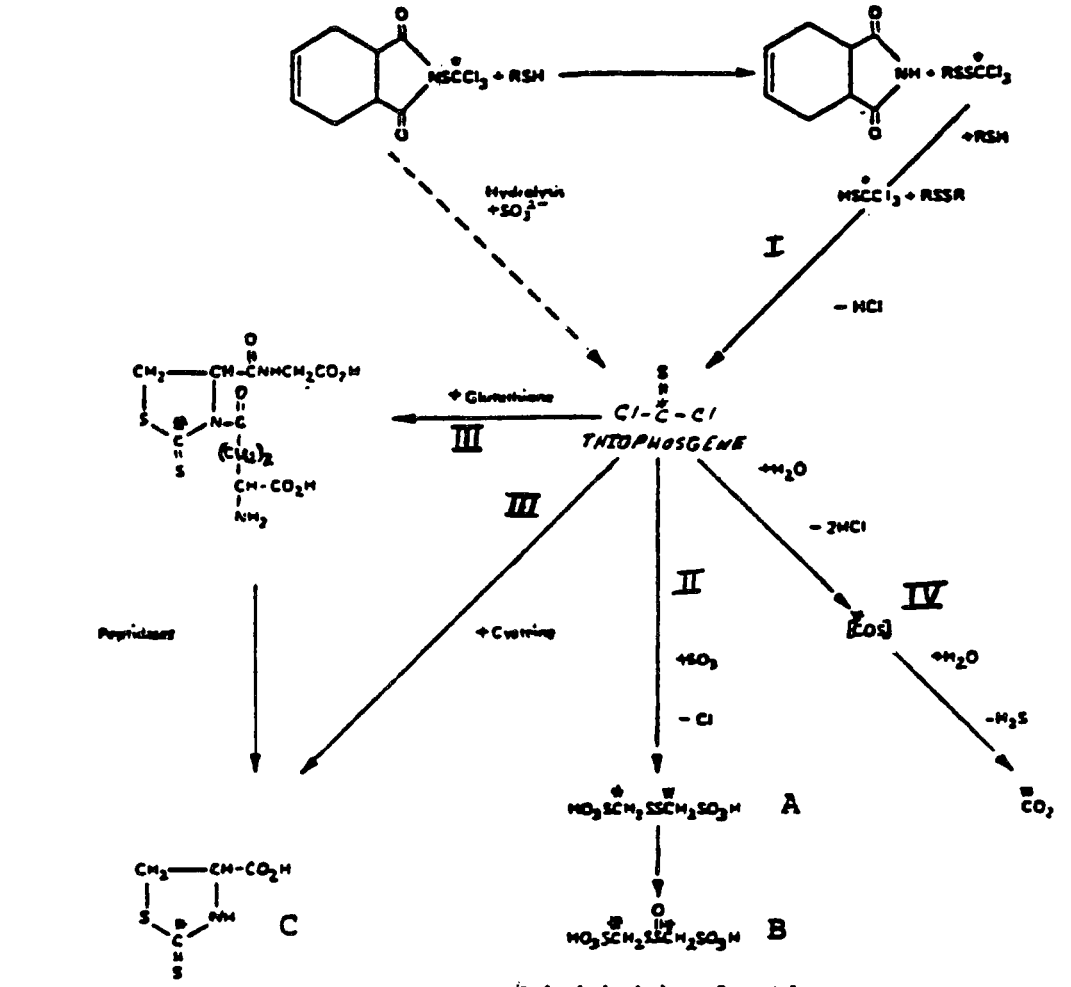


Figure 2. Proposed Metabolism of ^{14}C-Captan in the Rat

*C=^{14}C

intraperitoneal administration, metabolite C was the major urinary metabolite since neither metabolite A nor B was formed with this route of administration.

Tissue residue studies indicated that there was no organ-specific accumulation after oral administration and no significant difference between tissue residues in male and female rats. Total ^{14}C present in tissues 4 days after dosing was 0.6% of the dose of ^{14}C-captan. At day 8, only the bladder, kidney, and lung had a ^{14}C-content in excess of 1 ppm.

The differences between the rates of excretion and the difference in metabolic pathways in the gut after oral and intraperitoneal dosing indicate that captan is degraded in the gastrointestinal tract and that oral and intraperitoneal doses of captan may not be equivalently toxic.

Pharmacokinetic studies, using ^{35}S-captan were conducted by Seidler et al. 1971, in rats of unspecified strain. Of the ^{35}S in the single oral dose of ^{35}S-captan (either 143 or 390 mg/kg), 92% was excreted within the first 24 hours after dosing. (Of this amount, 38% was excreted in the feces and 55% in the urine.) On day 2, 5% of the ^{35}S was excreted (1% in the feces, 4% in the urine). A total of 101% ($\pm$8%) of the administered dose was recovered in the excreta within 3 days after dosing. As indicated above, DeBaun et al. (1974), found only 15.9% of radiolabel in the feces after an oral dose of 100 mg/kg ^{14}C-captan, whereas the result of Seidler et al., 1971, for fecal radiolabel was 38%. This discrepancy may be due to the possible use of different strains of rats, as well as the use of a dose almost four times that used by DeBaun et al. (1974). Larger amounts of ^{35}S-captan may not have been absorbed in the study of Seidler et al. (1971). In addition, the vehicle was not specified by Seidler et al. (1971), and may have affected the absorption.

On the basis of thin-layer chromatography and R_f values, a number of metabolites in rat feces and urine was identified which cochromatographed with known substances. Feces of rats dosed orally with ^{35}S-captan contained ^{35}S-captan, ^{35}S-glutathione, and an unidentified metabolite with an R_f value of 0.76. The urine contained ^{35}S-captan, ^{35}S-glutathione, the thiazolidine derivative of crysteine, and an unidentified metabolite with an R_f value of 0.76. Unmetabolized captan has not been detected in the urine in other studies; however, DeBaun et al. (1974) did detect unchanged captan in feces in preliminary metabolism studies utilizing a high dose (i.e., 650 mg/kg) of [trichloromethyl ^{14}C]captan. The presence of the ^{35}S-glutathione in the urine and feces may be accounted for by isotopic exchange between oxidized glutathione and ^{35}S-thiazolidine (Richmond and Somers, 1968). In fact, the interpretation of data based on the use of ^{35}S as a marker is difficult because isotope exchange occurs.

In tissue distribution studies, trace amounts of the S^{35} label were measured in various organs on the 1st day after oral administration. Concentrations (expressed as % of administered

dose) were: liver (0.45%), serum (0.04%), muscle (0.28%), kidneys (0.011%), brain (0.004%), and spleen (0.002%). On the 3rd day after administration, the amounts of the label increased in serum (0.05%), muscle (0.088%), kidneys (0.023%), brain (0.01%) and spleen (0.013%), and declined slightly in liver (0.041%). This finding was not apparent with a ^{14}C-label (DeBaun et al., 1974; Hoffman et al., 1973) with which the residues decreased after the single dose.

Another study utilizing ^{35}S-captan was conducted by Couch et al. (1977) in male Sprague-Dawley rats. A single dose of 6 mg/kg was administered intraperitoneally in 0.5 ml of corn oil to normal, sham-operated animals and to partially hepatectomized animals. In addition, multiple dose experiments were performed where three doses of 6 mg/kg were administered to sham-operated animals and to partially hepatectomized rats at 24-hour intervals. Excreta were collected every 24 hours, and tissue levels were measured at sacrifice (3 days after a single dose or 24 hours after the third multiple dose). After the single intraperitoneal dose, there was no difference in the percentage of label excreted by normal, sham-operated animals and by hepatectomized animals. After 24 hours, an average of 59.6% of radiolabel appeared in the urine, with 7.6% appearing in the feces. At 48 hours, the urine contained an average of 11.1% of the radiolabel and the feces contained an average of 3.9%. At 72 hours, the urine contained 5.3% and the feces 1.2%. The average total excretion over 72 hours was 76.0% in urine and 14.1% in feces. These results are consistent with the pharmacokinetics observed after intraperitoneal administration of 20 mg/kg ^{14}C-captan (DeBaun et al. 1974). The values reported by DeBaun et al. (1974) after 96 hours were 45.5% in urine, 5.8% in feces, and 18.4% in the expired air. Clearly, excretion of either ^{35}S- or ^{14}C-captan is much slower after intraperitoneal administration.

Levels of ^{35}S in the tissue of sham-operated rats were compared after single or multiple doses. The residue levels at 72 hours in the tissues after a single intraperitoneal dose were highest in the blood plasma (4.50 $\pm$ 0.65 ug of ^{35}S-captan equivalents) and spleen (3.00 $\pm$ 2.10); intermediate in the lung (1.80 $\pm$ 0.24), kidney (1.60 $\pm$ 0.12), and bone (1.30 $\pm$ 0.30); and lowest in the liver (0.71 $\pm$ 0.08), heart (0.52 $\pm$ 0.21), and brain (0.21 $\pm$ 0.02). The tissue levels after multiple administration were two or four times greater than the values obtained with single administration.

Captan treatment of isolated liver nuclei with 12 ug/ml of the ^{35}S-label for one hour resulted in binding to nuclear proteins. The degree of binding was 39% in acidic ribonucleoproteins, 14% in deoxyribonucleoprotein (including histones), 10% in nuclear sap protein, and 16% in "residual" protein fractions. In contrast to these in vitro studies, nuclei isolated from rat liver after animals had received multiple intraperitoneal doses of ^{35}S-captan contained exceedingly low levels of ^{35}S (i.e., 0.008 to 0.009 ug/g tissue). The data suggest that although the radiolabel can bind to protein components of genetic material and

possibly exert toxic effects, it is likely that very little of the ^{35}S actually reaches liver nuclei following administration to the whole animal due to metabolism, as judged by the low levels of radioactivity that were observed.

In a study in Swiss-derived CD-1 mice, the ability of orally administered captan to associate with DNA of several organs was investigated (Selsky, 1981). Mice were administered a single oral dose of 156 mg/kg of [^{14}C-trichloromethyl]captan of high specific activity (50-56 mCi/mmole) and the amount of ^{14}C associated with DNA from testis, duodenum, stomach, kidney, and liver determined 24 hours later. Values for the association of the radiolabel/DNA nucleotide molecule (expressed as the number of trichloromethyl carbon atoms/DNA nucleotide) ranged from 1.4-5.1 x 10^{-6} for testicular DNA to 1.4-1.8 x 10^{-5} for stomach DNA. The association levels among the different tissues were similar, and were not higher at sites of potential mutagenicity (i.e., testis) or carcinogenicity (i.e., duodenum) than at other sites. In those organs the radioactivity did not appear to be covalently bound to DNA since much of it could be lost from the DNA fraction upon dialysis against Tris-EDTA buffer. It should be noted that the identity of the radioactivity labeled moiety was not determined in this study. Furthermore, the dialyzable radioactivity may have been coprecipitated with the DNA and may not have actually been bound to that material. When preliminary experiments of a similar nature were performed in both mice and rats to evaluate ^{14}C-captan binding to tissue DNA by using higher doses of chemical (300 and 1600 mg/kg) but lower specific activities (0.19-1.9 mCi/mmole), no radioactivity was found associated with DNA (Selsky, 1981).

There is evidence that captan can inhibit hepatic microsomal hydroxylase activity in vivo. Truhaut et al. (1974) administered captan intraperitoneally at 10 mg/kg to male Sprague-Dawley rats. The hydroxylation of zoxazolamine was inhibited and paralysis time was significantly prolonged ($p < 0.01$).

Peeples and Dalvi (1978) showed that liver microsomes prepared from Sprague-Dawley rats given captan orally at 650 mg/kg and 100 mg/kg had diminished aniline hydroxylase activity. The hydroxylase activity was decreased by 10% at 100 mg/kg, and by approximately 50% at 650 mg/kg. When diethyl maleate, a liver glutathione inhibitor, was administered intraperitoneally in combination with 650 mg/kg captan administered orally, the aniline hydroxylase activity decreased a further 25%. Liver microsomes prepared from rats administered captan intraperitoneally at 20 mg/kg decreased the aniline hydroxylase activity 20%.

The *in vitro* effect of captan on rat hepatic microsomal cytochrome P-450 was studied by Dalvi and Ashley (1979). Captan at a concentration of 12 uM produced a 50% reduction of cytochrome P-450. This loss was not prevented by EDTA, which suggests that lipid peroxidation does not occur in captan metabolism, but was

prevented by the presence of reduced glutathione at a concentration of 0.5 mM.

Urbanek-Karlowska (1977) measured the activity of hepatic microsomal enzymes in relation to dietary protein and 0.1% captan fed in the diet. All rats on a 24%, 8%, or 4% protein diet and 0.1% captan for 8 weeks showed increased activity of p-nitroanisole demethylase. The rats on a 24%, 8%, or 4% protein diet and 0.1% captan for 12 weeks showed significant decreases in mean liver microsomal protein.

Other studies have examined the effect of captan on oxidative phosphorylation in isolated rat liver mitochondria. Nelson (1971a, b) demonstrated inhibition of succinate, glutamate, and B-hydroxy-butyrate supported active (state 3) respiration. The addition of cysteine partially reversed this effect. The inhibited enzymes all contain functional sulfhydryl groups. Nelson (1971b) also showed that captan affects the permeability of the mitochondrial membrane, resulting in mitrochondrial swelling. It is not clear whether the membrane effects are associated with the effects of captan on oxidative phosphorylation.

Engst and Raab (1973) administered a single dose of captan (route unspecified) at 5% of the LD_{50}. Blood was examined at 3 and 24 hours after dosing. Sulfhydryl groups in erythrocytes were reduced approximately 50% at 3 hours and 25% at 24 hours.

Summary of Metabolism Studies

Absorption of captan appeared to occur following oral administration as indicated by the appearance of radiolabeled material in the blood of lab animals. At 1 day after dosing, blood levels ranged from 2.95-21.8 ppm captan equivalents; at 8 days after dosing levels in blood declined to 0.4-0.98 ppm. At the earlier time period, most body excretory organs contained similar or greater concentrations of radioactivity than blood (e.g., 31.2-33.8 ppm in stomach and intestine; 6.1-42.9 ppm in kidneys and bladder; 4.2-17.7 ppm in liver; and 14.5 ppm in lung). After 8 days, only the kidney, bladder and lungs tended to have concentrations of radioactivity greater than that seen in blood. No unusual localization of radioactivity occurred in other body tissues.

Captan is extensively metabolized in the rat after oral administration. The initial step in the process appears to be hydrolysis of captan into two different parts, via cleavage of the N-S bond, to form THPI (tetrahydrophthalimide) and a derivative of the trichloromethylthio side chain. A major site of the hydrolytic cleavage of captan is the gastrointestinal tract, although the process also occurs in blood. The reaction is facilitiated in the presence of thiol compounds (e.g., glutathione and cysteine) and is pH dependent, accelerating as the pH increases (e.g., in moving from the stomach to the small intestine). For each of the two different metabolites formed by the hydrolysis of

captan, analysis of 0-48 hour rat urine has indicated the presence of a separate metabolic pathway. For the THPI pathway, the following four reactions occurred: (1) ring hydroxylation of THPI to 3-hydroxy THPI with further degradation to 3-hydroxy THPAM (3-hydroxy-trans-1-carboxy-2-carboxamido-4-cyclohexene) as the major reaction; (2) epoxidation of THPI to THPI-epoxide with further hydrolysis to 4,5-dihydroxy-THPI; (3) hydrolysis of THPI to THPAM; and (4) ring hydroxylation of THPI with subsequent rearrangement of the double bond to form 5-hydroxy-THPI. For the second pathway involving the trichloromethylthio side chain group, the following four reactions occurred: (1) conversion of the trichloromethyl-thio moiety to thiophosgene, a precursor for the remaining reactions; (2) condensation of thiophosgene with either free or peptide bound cysteine to form thiazolidine-2-thione-4-carboxylic acid; (3) reaction of thiophosgene with sulfite to form dithiobis (methanesulfonic acid) and its disulfide monoxide derivative: this is the major reaction after oral dosing but does not occur after intraperitoneal injection, indicating that it occurs in the gut; and (4) hydrolysis and/or oxidation of thiophosgene to CO_2. An analysis of feces for metabolites of captan has not been performed.

The major route of excretion is via the urine; additional excretion occurs in feces and expired CO_2. Over 4 days the total excretion of an orally administered dose of radiolabeled captan is approximately 80-92% (40-81% in urine, 7-40% in feces, and 0-23% in expired air). The rate of excretion after oral administration is rapid, with 50% of the total excretion occurring in the first 9 hours. After intraperitoneal injection, approximately 70-90% of an administered radioactive dose is also excreted over 3 to 4 days (45-76% in urine, 6-14% in feces, and 0-18% in expired air), but the rate of excretion is delayed with 50% of the total excretion occurring in the first 48 hours. Essentially all of the radioactivity found in the urine and feces after oral or intraperitoneal administration represents metabolites of captan with little or no unchanged captan present.

Differences in excretion pattern occurred with oral and intraperitoneal administration of radiolabeled captan. With intraperitoneal administration two metabolites normally seen after oral dosing, namely dithiobis (methanesulfonic acid) and its disulfide monoxide derivative formed by the reaction of thiophosgene with sulfite were not formed, and the rate of excretion was slower than with oral dosing. These differences suggest that captan is susceptible to metabolism in the gastrointestinal tract after oral administration.

An apparent difference in excretion pattern between the use of large and small oral doses of captan also occurred. Following the oral administration of 650 mg/kg of [trichloromethyl-^{14}C]captan, 28.7% of the administered radioactive dose was excreted in the feces, and unchanged captan was detected in the feces. In contrast, following the oral administration of lower doses of the radiolabeled captan (12 to 134 mg/kg), only 7.2 to 11.3% of the administered radioactive dose was excreted in the feces, and no

unchanged captan was detectible. The differences may reflect excretion of non-absorbed captan when high doses of the chemical are administered.

Conclusions

There are differences in the metabolic fate of captan if exposure occurs by any route other than the oral route. The data on intraperitoneal administration indicate both a slower elimination and different reaction products. For captan, the metabolic pattern after intraperitoneal administration is probably closer to the fate of the molecule administered dermally or by inhalation because gut metabolism is bypassed. Although absorption by the dermal and inhalational routes will initially enter the systemic circulation, captan entering by these routes will subsequently reach the liver where it will come in contact with high glutathione levels. Metabolism thereafter should be the same as that occurring after intraperitoneal administration.

The majority of the pharmacokinetic studies of captan were performed in rats, and only one pharmacokinetic study appears to have been performed in mice (Selsky, 1981). This study showed distribution of radioactive carbon throughout body tissues, including the tests. This may not be of biological concern because even though comparable levels of radioactivity were found throughout various body organs the only tumorigenic effect found in mice was confined to the intestine. Thus, it is likely that the radioactivity is not associated with a biologically active metabolite of captan.

THPI is present in both plants and animals as a captan metabolite and may be of toxicological concern. The Agency does not have sufficient data on residues of THPI to perform a risk assessment and will therefore be requesting such data pursuant to FIFRA 3(c)(2)(B).

5. Ecological Effects

a. Use

Captan is used as a fungicide on a variety of sites. For purposes of determining ecological effects, the major uses for captan are assumed to be apples, strawberries, potatoes, (seed piece treatment), soybeans (seed treatment), almonds and home gardens. For exposure analysis purposes these uses were considered representative of other uses (Stevens, 1982).

b. Environmental Chemistry

The half-life of captan in soil can range from one day to more than two months, depending on soil type and moisture. Under field conditions, two to three weeks is the expected half-life. Half-lives in water are reported to be approximately 12 hours between pH 2 and 6, 2.5 hours at pH 6-7, and 10 min.

at pH 8 and above. Captan effects on microbial populations are temporary if at all. Captan did not demonstrate a potential to bioaccumulate. Captan is not expected to leach.

c. Toxicity of Captan to Aquatic Organisms

The 96-hour LC_{50} values for various fish species exposed to captan technical (90-100% a.i.; Johnson and Finley, 1980) range from 49 (40.1-59.9) to 141 (119-167) ug/l. The rainbow trout (Salmo gairdneri) and bluegill (Lepomis macrochirus) 96 hour LC_{50} values are 73.2 (66.6-80.7) and 141 (119-167) ug/l respectively.

The MATC for fathead minnow is >16.5 to <39.5 ppb. The 48-hour LC_{50} for Daphnia magna is estimated to be greater than 7.1 mg/l (ABC, 1980).

Caldwell (1977) conducted a series of acute and chronic tests on various pesticides using the Dungeness crab (Cancer magister). The 96-hr LC_{50} values for the zoeal, juvenile and adult stages were each greater than 10 ppm. In chronic tests, the level at which captan significantly affected (1) egg hatch and pre-zoeal development is >10 ppm, (2) first stage zoeal motility 3.3 ppm, (3) continued zoeal survival 20 ppm, (4) juvenile survival >200 ppm and (5) adult survival >200 ppm.

Metcalf and Sanborn (1975) reported on a model ecosystem study designed to simulate the fate on captan in a farm pond. A 20 gal aquarium with a steeply sloping sand bottom was filled with 71 water at 26.5°C, and sorghum (Sorghum halopense) was planted along the bank. After plankton (diatoms, rotifers, etc.), Daphnia magna, mosquito larvae (Culex pipiens), algae (Oedogonium cardiacum), and snails (Physa spp.), were added to the water, radio-labeled captan - ^{14}C was applied to the sorghum seedings at 1.0 lb AI/acre, and slat marsh caterpillars (Estigmene acrea) were then put on the sorghum plants. Thirty (30) days after captan application, mosquitofish (Gambusia affinis) were added to complete the food chains. After a total of 33 days, samples were taken from the water, mud and remaining flora and fauna for residue analysis. No intact captan was identified in any sample.

d. Summary of Relative Risk to Aquatic Organisms

Although captan is very highly toxic to fish (96-hour LC_{50}'s $\leq$ 141 ppb), we believe that the available data provide an adequate basis for concluding that any nontarget aquatic effects, if any, are likely to be localized. There are no aquatic uses for captan and little movement of captan through leaching or runoff is expected. Additionally, captan hydrolyzes very rapidly in water (half-life up to one to two days, usually 1/2 day and less).

e. Toxicity of Captan to Terrestrial Wildlife

Schafer (1972) reports the acute oral LD_{50}'s of captan for red-winged blackbird (Agelaius phoeniceus) and starling (Sturnus vulgaris) to be greater than 100 mg/kg.

The dietary LC_{50} values for ring-necked pheasant (Phasianus colchicus) and mallard duck (Anas platyrhynchos) exposed to 95% technical captan are greater than 5000 ppm (Hill et al. 1975).

Atkins et al. (1973) reports that captan is "relatively nontoxic" to honeybees (Apis mellifera).

Hoyt (1969) reports that 10 days after applying captan at 0.75 lb/100 gal to apple orchards, there were no significant effects on the beneficial mite, Typhlodromus occidentalis. Croft and Nelson (1972) determined that captan at 2 lb/100 gal had "little activity" on adult female Amblyseius fallacis, another important predaceous mite in apple orchards. Nelson et al. (1973) studied the toxicity of various pesticides to a third important predaceous mite in apple orchards, Agistemus fleschneri. Captan, at 32 oz/100 gal was rather innocuous to this mite as well.

f. Summary of Relative Risk of Captan to Terrestrial Wildlife

Captan is relatively non-toxic to birds in dietary studies (LC_{50} >5000 ppm). Data are not sufficient to address with certainty the acute toxicity of captan to birds (LD_{50} >100 mg/kg). However, captan is not expected to be significantly hazardous to birds as a result of dietary or acute exposure. Residues on avian foodstuffs have been calculated to be quite low relative to toxicity.

Captan should pose no hazard to honey bees and other closely related hymenopterous pollinators.

Captan should pose no hazard to Typhlodromus occidentalis, Amblyseius fallacis, Agistemus fleschneri and other closely related predaceous mites.

No statement can be made at this time concerning the hazard of captan to mammalian wildlife.

C. RISK ASSESSMENT

The risk assessment process consists of four steps. In the first step, Hazard Identification, all relevant information is presented and a qualitative weight-of-the-evidence judgment is reached on the likelihood that the pesticide is a human carcinogen. In the second step, Dose-Response Assessment, experimental data are used in conjunction with certain assumptions and a mathematical model to extrapolate the likely upper bound of human cancer risk to the low dose range. The third step is Exposure Assessment in which human exposures via various routes and sources are estimated. Finally, in the fourth step, Risk Characterization, the results of the Exposure and Dose-Response Assessments are coupled to project the plausible upper bound of the cancer risk under different conditions of exposures. This step also includes a summary of the strength of the qualitative evidence, plus a treatment of the uncertainties in the final assessment.

1. Hazard Identification (Qualitative Risk Assessment)

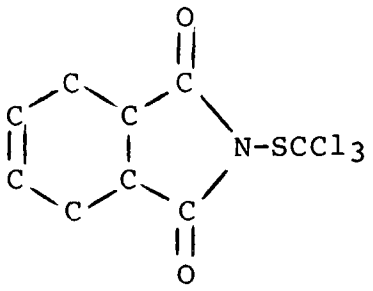
a. Structure-Activity Relationships

Captan is a protectant fungicide. The Agency has concluded that at least two other fungicides with similar structural relationships are oncogenic in laboratory animals.

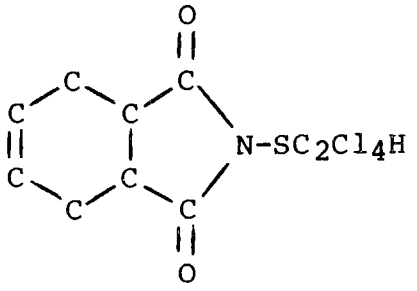
Folpet, also known as phaltan (N-[(Trichloromethyl)thiol] phthalimide was administered in the diet of CD-1 mice at 1000, 5000, and 12000 ppm (Chevron, 1982a). A dose-related increase in the incidence of intestinal adenomas and adenocarcinomas, as well as in mucosal hyperplasia of the small intestine in both male and female CD-1 mice was observed. These proliferative changes occurred with the greatest frequency in the duodenum, being more prevalent proximal to the pyloric sphincter and decreasing with distance distally in the small intestine, as shown by a lower frequency in the jejunum and no neoplasms, but only mucosal hyperplasia, in the ileum.

Captafol, also known as difolatan (cis-N-[1,1,2,2-Tetrachloroethyl)thiol]-4-cyclohexene-1,2-dicarboximide) has produced tumors of a different type and location than captan [liver and mammary gland tumors in female rats (Charles River Crl: CD Sprague Dawley BR) and lymphosarcomas, myeloproliferative disease and hemangiosarcomas in both sexes of mice (CD-1) (Chevron, 1982)].

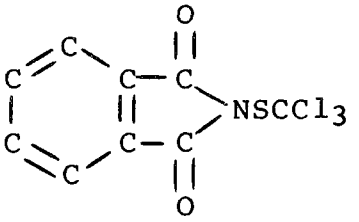
Since intestinal tumors were seen in the folpet-treated but not the captafol-treated CD-1 mice, it is likely that the highly reactive electrophile, thiophosgene (the initial metabolite derived from the one carbon side-chain of captan and folpet) is responsible for the intestinal tumors produced by captan and folpet.



Captan



Captafol



Folpet

b. Metabolic and Pharmacokinetic Properties

The metabolic an pharmacokinetic properties of captan were discussed in section II.B.4 of this document.

c. Non-oncogenic Toxicological Effects

Over the past 30 years the acute and subacute toxicity of captan has been studied extensively in a large number of animal species, including rats, swine, sheep, cattle, chicken, hamsters, rabbits and monkeys (EPA Substitute Chemical Program, April 1975). These studies show that captan is not acutely toxic, e.g., rat LD_{50} > 5 g/kg. In repeated dosing studies, captan could be tolerated without ill effects at high exposure levels. These studies, overall, provide no additional insight on captan's oncogenic potential.

d. Short Term Tests - Mutagenicity

1) Microbial or In vitro Cell Culture Evidence For the Intrinsic Mutagenicity of Captan

Evidence (which was not rebutted) was presented in the Agency's PD 1 to show the ability of captan to produce mutagenic events in bacteria, eukaryotic microorganisms, and mammalian cells in culture. Specifically, captan has been shown to induce gene mutations in Escherichia coli WP2, Salmonella typhimurium G46, TA1950, TA1530, TA1535, TA1537, TA100, TA 98, and Aspergillus nidulans. Gene mutations were also produced in chinese hamster ovary V-79 and lung fibroblast cells in culture.

An effect on DNA was indirectly shown by induction of DNA repair or differential toxicity in bacterial strains lacking DNA repair mechanisms in E. coli WP2, Bacillus subtilis, Aspergillus nidulans, Saccharomyces cerevisiae, and the following in vitro mammalian cells in culture: SV40 transformed human fibroblasts, chinese hamster lung fibroblasts, and in chinese hamster ovary V79 cells (this last study, Tezuka et al. 1980, was not included in the PD 1.)

Captan produced chromosome aberrations in cultured (in vitro) human embryo lung cells, rat kangaroo cells, and in chinese hamster ovary V79 cells (Tezuka et al. 1980).

2) Reduction of Mutagenicity of Captan in the Presence of Liver Enzyme Systems or Free Sulfhydryl Groups

In addition to the positive effects summarized above, captan was inactive in other studies. In general, captan produced mutagenic events only in the studies lacking a metabolic activation system. When a metabolic activation system was included the mutagenic activity of captan was greatly reduced or undetectable. Several studies examined this effect in detail:

Ficsor et al. (1977) found approximately a 33% reduction in reverse mutations in S. typhimurium TA100 after incubation with rat liver S9 microsomal mixture. Similarly, Marshall et al. (1976) found a reverse mutation reduction of approximately 50% in S. typhimurium TA1535 and TA1537. This decrease in activity was also reported in the assays by Simmon et al. (1977) in S. typhimurium TA100 and TA1535.

Ficsor et al. (1977) also performed host mediated assays in which captan was injected subcutaneously in mice or given orally to rats. Bacteria injected intraperitoneally were later isolated and tested for mutation induction. In another experiment they performed, blood and urine from mice treated orally with captan was tested for mutagenic metabolites by means of a bacterial reverse mutation spot test. None of these assays showed any mutagenic activity due to the metabolized captan. In a final set of experiments, a reverse mutation assay with S. typhimurium TA1535 was used to test the mutagenicity of captan preincubated with human blood, rat blood, or rat plasma. In the presence of rat blood, mutagenicity was reported at 5000 and 10,000 ug captan/ml but not at 1000 and 500 ug captan /ml. The results for human blood were similar. Mutagenicity was seen when 20 ug captan/ml was preincubated with rat plasma but not at a dose level of 200 ug captan/ml.

This effect was also examined in an experiment (Moriya et al. 1978) not reported in the Position Document 1. They found that reverse mutations induced in E. coli WP2 hcr and S. typhimurium TA1535 by 0.15 uM captan/plate were greatly reduced or undetected by preincubation of captan with rat liver homogenate (both with and without the cofactors needed to activate the enzymes), cysteine (an amino acid with free sulhydryl groups), or whole rat blood. When captan was preincubated with four concentrations of cysteine from 0.5 to 5.0 uM cysteine/uM captan a dose response was seen (no mutagenic activity was seen at 5.0 uM cysteine).

Swenberg et al. (1976) found that the activity induced by captan in an alkaline elution DNA damage study in Chinese hamster

lung fibroblast cells in culture was not detected in the presence of an S9 microsomal mixture metabolic activation system.

3) Mutagenicity of Captan in In Vivo Experiments

No chromosome aberrations were seen in bone marrow preparations after Wistar rats were given single doses of 500, 1000, or 2000 mg/kg captan by gavage or after five consecutive daily doses of 200, 400, or 800 mg/kg (Tezuka et al. 1978).

Several dominant lethal tests were performed and all reported negative results except for one. Dominant lethal effects were reported in Osborne-Mendel rats and CBA-J mice by T.F.X. Collins (1972a). Captan was given for 5 days by intraperitoneal injection in doses of 2.5, 5.0, and 10 mg/kg/day or by oral intubation in doses of 50, 100, and 200 mg/kg/day to groups of 15 rats and 15 mice. The mice were mated with two virgin females each week for 12 weeks. Caesarean sections were performed on the 13th day of pregnancy for the rats and on the 12th day for the mice.

There were significant increases ($p<0.05$) in the number of early fetal deaths per pregnancy among the potential offspring of mice given 200 mg/kg/day intraperitoneally and mated 4 and 5 weeks later. Similar increases in the number of early deaths per pregnancy were reported among the offspring of mice given 100 mg/kg/day and 200 mg/kg/day orally and mated 1 and 2 weeks later.

The groups of mice given captan at the highest doses showed significant increases ($p<0.01$) in the percentage of litters with 2 or more early fetal deaths for matings on week 5 after intraperitoneal administration and on week 1 after oral gavage.

Significant increases ($p<0.05$) were found in the mean number of early deaths per pregnancy for those pregnancies sired by rats 4 weeks after the rats were given captan orally at a dose of 100 mg/kg/day. Increased early fetal deaths were also found in pregnancies sired by rats at 1, 2, and 5 weeks after treatment with 200 mg/kg/day captan. When the litter was considered an experimental unit and affected litters were defined as those with at least one early fetal death, a significant increase ($p<0.05$) in the number of affected litters was seen in the rat test group given 100 mg/kg/day orally and mated after 4 weeks. The other two dose groups showed consistent increases in the numbers of affected litters. In addition, there were significant linear dose response relationships in affected litters from rats mated 3 and 4 weeks after treatment.

When "affected litters" were defined as those with two or more early deaths, the data showed a significant increase ($p<0.05$) in the number of affected litters for rats given a daily oral

dose of 100 mg/kg captan and mated 2 and 5 weeks later, and ($p<0.01$) for rats given a daily dose of 200 mg/kg captan, and mated 1, 2, and 5 weeks later.

To summarize both the rat and mouse studies (Collins, 1972a), significant linear dose responses were seen for different weeks of mating for various combinations of species and routes: intraperitoneally treated rats mated in weeks 4 and 5; orally treated rats mated in weeks 1 and 2; intraperitoneally treated mice mated in weeks 1 to 3 and 5 to 7; and orally treated mice mated in weeks 1 to 5 , 9, and 12.

There are several problems with this study when considering it for use in a risk assessment. The direct intraperitoneal or oral gavage exposure gives the animal an exposure that does not relate to a dietary exposure, especially considering the metabolic and mutagenicity (both microbial and in vitro) evidence for reduction of mutagenic activity. The response is peculiar in that no consistant pattern of spermatogenesis stage effects are seen. The raw data is unfortunately no longer available to reevaluate these effects.

Collins (1972b) also performed a 2-generation "reproduction fitness" study in DBA/2J mice. It was designed to show both dominant lethal and polygenic (mutagenic) effects. Two groups of 110 male mice received gavage doses of 50 or 100 mg/kg of captan for 5 days. Each treated male was mated with 2 untreated females for 3 weeks to produce F_1 offspring, and the latter progeny were subsequently mated to yield F_2 offspring. Significant changes induced by captan included a decreased viability index (number newborn/total number born) in F_1 males and females at 50 and 100 mg/kg; decreased weaning weights in F_1 and F_2 (first litter) males and females at 50 and 100 mg/kg; and a decreased survival index (number of survivors to day 4/number newborn) in F_1 and F_2 (first litter) males and females at 100 mg/kg.

It is difficult to make a biological interpretation of these results. On the basis of this test alone, it would appear that captan could induce some type of polygenic effect in mice although reevaluation of the data would be difficult due to incomplete test description and lack of the raw data or parameters such as standard error. This particular assay in mice is highly experimental and has not been found to be reliable. Even X-rays, which should provide a worst-case control, have produced equivocal, non-reproducible, results in mice. As in the dominant lethal experiment (Collins, 1972a), the oral gavage dosing does not realistically reflect the normal oral exposure. The raw data for this experiment is also no longer in existence.

A study by Tezuka et al. (1978) was designed to verify the dominant lethal Collins' study using a similar protocol in male C3H and female SLC-ICR mice, but no dominant lethal effects were found. The Agency found fault with the report in the

literature as stated in the PD 1, (the protocol was inconsistant and unclear as reported) however additional information submitted by Dr. Shirasu, one of the authors, shows this study to be acceptable. Groups of 15 male mice were treated by oral gavage with 5 daily doses of 200 or 600 mg/kg captan. Each male was mated with one female at 2 to 4 days intervals. The mating was controlled to obtain a maximum of 2 copulated females per male per week for 6 weeks.

Simmon et al. (1977) in an EPA sponsored study administered captan to ICR/SIM mice in the diet at up to 5000 mg/kg/day for 7 weeks. No increase in the frequency of dominant lethal mutations were seen.

A heritable translocation study was performed by Stanford Research Institute (SRI) for EPA (Simmon et al. 1977). This study was described in the PD 1. One translocation was found in the high dose group which would normally be sufficient to classify captan as positive for heritable translocations; however, one translocation was also seen in the negative control group. This study has been evaluated as negative, equivocal, or positive at various times by different groups. Since the Position Document 1 was published, however, a committee of the experts in the field of heritable translocation testing was formed by EPA as part of the Gene Tox program. This group was charged with evaluating all heritable translocation tests available to them. This group of experts has evaluated the SRI captan heritable translocation study as negative (Generoso et al. 1980).

A mouse color coat spot test was submitted to the Agency by Chevron Chemical Company as part of their rebuttal. It was performed by Litton Bionetics, No. 20951, October, 1980. The mouse spot test crosses strains of mice so that the embryos are heterozygous for several coat-color markers. The embryos are exposed to the test substance in utero by treating females during gestation. Mutations induced in these heterozygous melanocyte somatic embryo cells may be manifested (as the cells develop into clones on the skin) as variously colored spots on the newborn mice. These mutations may be due to both chromosome damaging or gene mutational mechanisms.

T-strain males, genotype (a/a,b/b,$c^{ch}p/c^{ch}p$,d se/d se, s/s) from Oak Ridge National Laboratory Tennessee were mated daily with 2 female C57BL/6J mice, genotype (a/a), from Charles River, Wilmington, MA. Mating was continued until sufficient females were obtained for the experiment.

Fifty to fifty-two pregnant female per group were treated with 0, 100, 1000 and 5000 ppm captan in the diet on days 8, 9, 10, 11, and 12 of gestation. Twenty six females were treated with ethylnitrosourea (ENU) as the positive control group. The incidences of recessive somatic mutation spots were 2.9, 4.4, 2.2, and 1.9% respectively for 0, 100, 1000, and 5000 ppm

captan. ENU induced 19.4% recessive somatic mutation spots. This study may be considered negative for captan.

4) Risk of Heritable Mutations

In order to have concern for transmission of heritable mutagenic events, it must be shown that:

(a) The chemical is an intrinsic mutagen; e.g. that it is able to affect DNA and cause a mutagenic event.

(b) The chemical is able to reach the gonads in an active form.

(c) Mutations induced in gonadal cells are transmitted through offspring.

In the case of captan, it is evident that it has intrinsic mutagenic properties. This mutagenicity, however, is diminished or absent in vivo at normal exposure levels.

The mutagenic endpoints of concern for captan are gene mutations and chromosome aberrations. For gene mutations, captan has been demonstrated to have intrinsic mutagenicity in microbial systems and in in vitro cell assays. In a relatively sensitive in vivo system (the mouse coat color spot test), however, no mutagenicity was detected. This is one of the few in vivo systems which will detect gene mutational events. It is a somatic cell system and is not capable of determining if a mutation is heritable. The only other test that could be performed at this stage in order to assess gene mutational heritable risk is the mouse specific locus test. The mouse specific locus test is less sensitive than the spot test when performed with any reasonable number of animals; therefore, it is not expected to detect any mutational events with captan.

For chromosome aberrational events, the dominant lethal test is capable of detecting mutations in gonadal cells in the male. A positive dominant lethal test shows that the chemical reaches the gonads in an active form. Equivocal results are seen in these tests for captan. All of the well conducted tests are negative; however, the Collins' dominant lethal tests were reported as positive. The Agency does not have complete confidence in these results, but for the purposes of this risk assessment, it is provisionally considered as a positive test. To assess heritable risk, it must now be determined if the mutational event may be transmitted to future generations. The best developed assay available to us is the heritable translocation test. The dominant lethal assay does not reveal heritable events since the event measured is lethality and is therefore not usable for quantitative risk assessment. The heritable translocation test has been shown to be negative.

Captan has been shown to be mutagenic in in vitro experiments in lower organisms, but the results are equivocal in the in vivo experiments. The Agency concludes that captan is either non-mutagenic in vivo or possesses such a low mutagenic capacity in the in vivo assays used for quantitative heritable mutagenic risk assessment that it is not possible to detect its mutagenic activity. Although captan may be able to cause somatic mutational events and may, therefore, have an oncogenic problem, the risk to humans of heritable mutagenicity is extremely low or does not exist and does not warrant further testing at this time.

e. Long-Term Animal Studies - Oncogenicity

1) Summary of Pertinent Studies in Animals

The analysis of three captan chronic feeding studies showed a dose-tumor relationship yielding an average (geometric mean) potency of $Q_1^* = 2.3 \times 10^{-3}$ (for dose in mg/kg/day) with a weight of evidence classification B2 (probable human carcinogen) under the draft EPA guidelines (U.S. EPA, 1984, 49 FR 46294). This potency factor is based on adenomas and adenocarcinomas of glandular cell origin in the gastrointestinal tract of both sexes of mice in three studies and on kidney tumors in male rats.

(a) Innes et al. (1969)

Innes et al. (1969) studied 120 chemicals and 10 control compounds which were tested in two hybrid strains of mice. Eighteen mice/strain/compound were administered the maximum tolerated dose (MTD) by gavage from day 7 to day 21. The study mice were then fed test or control compound mixed in with their daily diet until death or sacrifice, at 18 months of age. The captan treated mice were administered 215 mg/kg/day by gavage and later 560 ppm in their diet. No increase over control incidence of liver, lung, or lymphoid cell tumors was detected at the $p \leq .05$ level of statistical significance.

(b) National Cancer Institute (1977)

The National Cancer Institute (1977) study, "Bioassay of Captan for Possible Carcinogenicity" was conducted by Gulf South Research Institute using 50 animals per treated group and 10 concurrent controls per sex per species of B6C3F1 mice and Osborne-Mendel rats. The dosing schedules followed for mice are found in Table 1.

The NCI report evaluated the B6C3F1 mouse pathology findings as quoted below (excerpts from NCI (1977) pp. 27 and 29-31).

> "With the exception of the proliferation and/or neoplastic lesions observed in the duodenum of both male and female treated mice, the pathological changes

Table 1 - Design of Captan Chronic Feeding Studies in B6C3F1 Mice (NCI, 1977)

Sex and Treatment Group	Initial No. of Animals[a]	Captan in Diet (ppm)	Time on Study: Treated (weeks)	Time on Study: Untreated[b] (weeks)
MALE				
Matched-Control	10	0		91
Low-Dose	50	8,000	80	
		0		11
High-Dose	50	16,000	80	
		0		11
FEMALE				
Matched-Control	10	0		90-91
			80	
Low-Dose	50	8,000		
		0		11
High-Dose	50	16,000	80	
		0		11

[a]All animals were 35 days of age when placed on study.

[b]When diets containing captan were discontinued, all treated mice and their matched controls were fed the control diet (2% corn oil added) until termination of the study.

observed were not considered to be related to the administration of captan.

The duodenum lesions were located approximately 1 cm posterior to the pylorus, usually in the antimesenteric portion of the duodenal muscosa. Grossly, they were either single, well-circumscribed (3-5 mm across) and slightly elevated (1-2 mm) areas, or single, thin mucosal projections up to 5 mm in height. The lesions were inconspicuous on the serosal surface. Microscopically, the following three different lesions were classified:

(1) mucosal hyperplasia -- a proliferation of glands and villi epithelium,

(2) adenomatous polyp -- a more accentuated proliferative process with glandular structures and villi aggregated and branched around supporting stalks made up of connective tissue (features of malignancy were not observed), and

(3) adenocarcinoma (polyploid carcinoma) -- one of the most advanced and aggressive-appearing lesion, consisting of cellular anaplasia with numerous mitotic figures, disorganized microacini, and areas where focal neoplastic infiltration was evident.

Tinctorial changes (basophilia) were also present.

The classification of these lesions was frequently difficult. Nevertheless, the location and some common cellular characteristics suggest that they are different development stages of the same type of lesion. The distribution and incidence of the duodenal alteration were as follows:

	Male Mice			Female Mice		
	Controls	Low Dose	High Dose	Controls	Low Dose	High Dose
Number examined	(9)	(43)	(46)	(9)	(49)	(48)
Adenocarcinoma	0	1	3	0	0	3
Adenomatous polyp	0	2	2	1	1	0
Mucosal hyperplasia	0	0	3	0	0	0

The rarity of these lesions in the strain of mouse used suggests that the lesions were caused by captan.

The incidences of adenocarcinoma of the duodenum showed a significant linear trend for both male and female mice, with Cochran-Armitage probability levels of 0.033 and 0.022, respectively, using the pooled controls. The Fisher exact test results for both sexes are not significant.

> When the incidences of adenocarcinoma of the duodenum are combined with those of adenomatous polyp, not otherwise specified, for statistical analysis, the tests for male mice show a substantial increase in significance when compared with pooled controls. The test for positive linear trend is significant (P = 0.008), the Fisher Exact Test in the high dose male mice has a probability level of 0.009, and the 95% confidence interval for relative risk has a lower limit of 1.849 using pooled controls. The incidence of these combined tumors in female mice is not significant. The overall consideration of these various statistics suggests a dose association of the test chemical with tumors in the duodenum in male mice."

Table 2 presents the design of the chronic feeding study in rats. In NCI's evaluation of the Osborne-Mendel rat pathology, they state:

> "In rats, there was a positive dose-related trend (P = 0.047) for the combined incidence of cortical adenoma and the cortical carcinoma of the adrenal gland in high-dose females compared with the incidence in the pooled controls... (pooled controls 0/64, low dose 2/50, high dose 3/47).... However, the spontaneous incidence is variable in this strain of rat, and the incidence of tumors was very low; one adrenal cortical adenoma and one carcinoma were found in the low-dose animals and two adrenal cortical adenomas and one carcinoma in the high-dose group. There was also a positive dose-related trend for the incidence of C-cell adenoma of the thyroid in female rats (pooled controls 1/66, low-dose 1/49, high-dose 4/44, P = 0.035). The relationship of these tumors to treatment is not clearly established."

The individual animal data of this study have not been reviewed to verify the NCI report tables or statistics, either by Chevron or by the Agency. The findings in the mouse were considered by Chevron to be an unusual or false positive finding. Accordingly, Chevron replicated the NCI study in a different strain of mouse.

(c) High-Dose Mouse Study (HDS) (Chevron, 1981)

The Chevron (1981) study differed from the NCI (1977) study in several respects: the average daily dose differed slightly; the dosing schedule was increased at week 5 of the study and continued at the revised level until planned kill after 113 weeks of feeding (when the animals were approximately 120 weeks of age); and CD-1 mice were used as the experimental animal. The experiment was performed at a different laboratory so that all environmental factors and study personnel differed.

There were 80 animals per sex per dose including 80 concurrent controls per sex. The study design is found in Table 3. The

Table 2 - Design of Captan Chronic Feeding Studies in Rats (NCI, 1977)

Sex and Treatment Group	Initial No. of Animals[b]	Captan in Diet (ppm)	Time on Study: Treated (weeks)[c]	Time on Study: Untreated (weeks)[d]	Time-Weighted Average Dose[e] (ppm)
MALE					
Matched Control[a]	10	0		114	
Low Dose	50	4,000	21		
		2,000	59		2,525
		0		33	
High-Dose	50	8,000	41		
		4,000	39		6,050
		0		34	
FEMALE					
Matched-Control[a]	10	0		114	
Low-Dose	50	4,000	21		
		2,000	59		2,525
		0		33	
High-Dose	50	8,000	41		
		4,000	39		6,050
		0		34	

[a]The matched controls consisted of 5 animals of each sex, started with the low-dose animals, and 5 animals of each sex, started with the high-dose animals.

[b]All animals were 35 days of age when placed on study.

[c]Doses of captan were lowered at week 21 during the study, since it was believed that excessive mortality might occur before termination of the study based on the mortality, weight changes, and general condition of rats used in similar bioassays of other chemicals at Gulf South Research Institute.

[d]When diets containing captan were discontinued, the high-dose rats and their matched controls were fed the control diet without corn oil for 6 weeks, then the control diet (2% corn oil added) for an additional 28 weeks, while low-dose rats received only the control diet (2% corn oil added) until termination of the study.

[e]Time-weighted average dose = $\frac{\text{(dose in ppm x no. of weeks at that dose)}}{\text{(no. of weeks receiving each dose)}}$

Table 3 - High-Dose Mouse Study Design (Chevron, 1981)

Group	Dose (ppm) Weeks 1-4	Weeks 5-113	Time Weighted Average
I	0	0	0
II	2,000	6,000	5,858
III	6,000	10,000	9,858
IV	10,000	16,000	15,788

pathologist (W.L. Spangler) used the terminology "adenoma" and "adenocarcinoma" to designate the benign and malignant forms of duodenal and other intestinal neoplasms of glandular cell origin.

During the HDS, no unusual diseases or complicating factors were observed.

Survival appears dose-related as can be seen from the "at risk" mortality data given in Table 4.

Table 4 - High-Dose Mouse Study Mortality Rates (Chevron, 1981)

(Number of Deaths/Number of Animals at Risk)

MALES

Time Interval (weeks)	Dose (ppm) 0	6,000	10,000	16,000
0-52	5/80	3/80	4/79	8/80
53-75	9/75	12/77	16/75	16/72
76-90	14/66	8/65	12/59	28/56
Survivors	52	57	47	28

FEMALES

Time Interval (weeks)	Dose (ppm) 0	6,000	10,000	16,000
0-52	4/80	3/80	4/80	4/80
53-75	8/76	6/77	5/76	17/76
76-90	17/68	11/71	10/71	30/59
Survivors	51	60	61	29

In males there is a statistically significant dose related trend in mortality which is best demonstrated by examining dosed animals only. The survival pattern of females is less clear but is still statistically significant due to the higher

mortality in the high dose (16,000 ppm) group. Using Peto's trend test (Peto, 1980) $P < .0001$ for males and .0003 for females.

With respect to the duodenal tumors, the Chevron (1981) report shows the following in their "Table 4" (Volume I of VII of the Chevron report):

"Socal Table 4"

	Males				Females			
Duodenum	Control	Low	Mid	High	Control	Low	Mid	High
Number Examined[a/]	74	73	72	75	72	78	76	76
Number with duodenal neoplasms	2	20	21	39	2	24	19	29
Adenocarcinomas[b/]	1	10	14	30	0	17	14	20
Adenoma[b/]	1	11	7	11	2	10	8	12
Undifferentiated Sarcoma	0	1	0	0	0	0	0	0

a/ Excluding severely autolyzed and missing tissues.

b/ Tabulated by total number of neoplasms; some animals had multiple (i.e., both benign and malignant) neoplasms.

Note: the doses are Control = 0; Low = 6000 ppm; Mid = 10000 ppm; and High = 16000 ppm.

The Agency review of the individual mouse data reveals that while there were a number of animals where gastrointestinal tract tissue was autolyzed, the Socal pathologist, Dr. W.L. Spangler, was able to diagnose pathological changes when they were present. Therefore, the denominators used in this report exclude only animals where digestive tract tissue was reported as missing. Secondly, the 19 individual animals among the low-dose males were diagnosed with adenoma or adenocarcinoma of the duodenum - the 20th mouse reported in this study had only an undifferentiated sarcoma. The 19 included 8 animals with adenocarcinomas only, 9 with adenoma only and 2 with both.

Statistical evaluation of the adenoma-adenocarcinoma incidence data from the High-Dose study showed statistically significant dose related trends in both sexes for the summary data displayed in "Socal Table 4" and for the time-weighted trends of these findings. The Exact Test also indicates that the incidence in all treated groups is statistically greater, $P<.01$, than the incidence observed in the control group.

(d) Low-Dose Mouse Study (LDS)(Bio/Dynamics, 1983)

The primary purpose of this study (done by Bio/dynamics, 1983, for Chevron) was to characterize the response of the gastrointestinal tract to captan in mice. This is illustrated by the restricted number of tissues taken and the detailed specific instructions for removal, handling, preparation for gross and microscopic examination of the entire gastrointestinal tract. Test animals were Charles River CD-1 mice (ICR derived). The experimental design utilized five dose levels (0, 100, 400, 800, 6,000 ppm) of captan with 100 mice of each sex being randomly assigned to each dose level. No unusual diseases or complications were observed.

Although there was an unusually high mortality among control animals, there is evidence of a mortality-dose related trend (but not as strong as in the HDS). These findings are shown in Table 5.

Table 5 - Low-Dose Mouse Study Mortality Rates (Bio/Dynamics, 1983)
(Number of Deaths/Numbers of Animals at Risk)

MALES

Time Interval (weeks)	Dose (ppm)				
	0	100	400	800	6,000
0-52	7/100	4/99	4/100	5/100	13/100
53-75	38/93	32/95	24/96	31/95	54/87
73-88	23/55	32/63	43/72	32/64	24/33
Survivors	22	31	29	32	9

FEMALES

Time Interval (weeks)	Dose (ppm)				
	0	100	400	800	6,000
0-52	12/100	6/100	4/100	8/100	3/100
53-75	22/88	22/94	17/96	16/92	28/97
73-88	24/66	26/72	32/79	26/76	29/69
Survivors	42	46	47	50	40

Using Peto's trend test (Peto, 1980) on the above data shows a statistically significant dose related increase in male mortality rates, $P<.01$; but no important effect among females, $P<.21$.

Although this study was planned to run for two years (104 weeks) it ended at about 96 weeks due to the poor survival. However, the tissues from the gastrointestinal tract of all animals were examined. Separate tables were provided by Knezevich for hyperplastic lesions of the duodenum (Bio/Dynamics Table A) and jejunum/ileum (Table B); and neoplastic lesions characterized as "adenoma/polyp(s)", "carcinoma primary", "squamous cell carcinoma", and leiomyosarcoma" of the stomach (Table C), duodenum (Table D), jejunum/ileum (Table E), and cecum/colon (Table F). No discussion was provided by Bio/dynamics of the overall gastrointestinal response but animals appearing in two places on one table or in multiple tables were identified. These tables are not reproduced in this document.

In reviewing the data from this study, the Agency followed the guidance by National Toxicology Program (NTP) scientific counselors report (NTP, 1984). Only animals with adenoma or adenocarcinoma (carcinoma) of the glandular cells were used, moreover, to make the data in this report comparable with the high-dose study the 2 females with cecum or colon polyp or carcinoma were omitted. One of these, the control female with carcinoma could not be verified by examination of the raw data (i.e., individual animal pathology studies).

The Agency recount of animals with adenoma/polyp and/or carcinoma of glandular cells of the gastrointestinal tract are shown in Table 6.

Table 6 - Diagnosis of Gastrointestinal Tract Glandular Tumors for Stomach, Duodenum, and/or Jejunum/Ileum (Bio/Dynamics, 1983)

Females					Diagnosis	Males				
0	100	400	800	6,000	Dose Groups	0	100	400	800	6,000
0/100	1/100	3/100	3/100	5/100	Adenoma/polyps	0/100	6/100	1/100	1/100	4/100
0/100	0/100	0/100	0/100	2/100	Carcinoma	0/100	0/100	0/100	0/100	1/100
0/100	1/100	3/100	3/100	7/100	Either	0/100	6/100	1/100	1/100	5/100

The incidence of adenoma and carcinoma of the glandular cells of the gastrointestinal tract demonstrated a statistically significant dose-related response ($P<0.01$) in female rats. In addition, the Fisher's Exact Test comparing high-dose incidence with controls shows a statistical significance of $P<0.025$ in females. However, in males no dose response trend was noted. The Fisher's Exact Test comparing the 100 ppm group with controls shows a statistical significance of $P<0.05$.

(e) Rat Study (RS) (Stauffer/Chevron, 1982)

This study was carried out by E.F. Goldenthal and L.W. Nelson of the International Research and Development

Corporation (IRDC) for Stauffer Chemical Company starting October 4, 1978, and terminating 2 years later on October 3, 1980 (Stauffer/Chevron, 1982). Test animals were Charles River CD rats.

The experimental design specified four dose levels (0, 20, 100, 250 mg/kg/day) of captan fed to 70 rats of each sex per level for a duration of 2 years. No unusual diseases or complications were observed. The survival rates are of interest. Table 7 shows the results of the rat survival and mortality rates in this study.

Table 7 - Rat Study Mortality (Stauffer/Chevron, 1982)
(Number of Deaths/Numbers of Animals at Risk)

MALES

Time Interval (weeks)	Dose (ppm)			
	0	25	100	250
0-52	2/70	3/70	3/70	3/70
54-78	5/58	3/57	3/57	9/57
80-88	3/43	4/44	6/44	5/38
90-96	4/40	7/40	7/38	7/33
Survivors	36	33	31	26

FEMALES

Time Interval (weeks)	Dose (ppm)			
	0	25	100	250
0-52	2/70	1/70	1/70	3/70
54-78	1/58	7/59	3/59	7/57
80-88	4/47	7/42	4/46	2/40
90-96	4/43	6/35	5/42	3/38
Survivors	39	29	37	35

There is a statistically significant, $P<.025$, dose related trend in mortality for males but not for females (Peto's test for trend).

In the male rats, the data demonstrate a statistically significantly increasing trend for kidney tumors (benign and malignant combined), 1/70 controls, 1/70 fed 25 mg/kg/day, 3/70 fed 100 mg/kg/day, and 4/70 fed 250 mg/kg/day; as shown

by the Armitage trend test P<.05. The results of the findings are shown in Table 8, which indicates that progression to malignancy was not predominate.

Table 8 - Summary of Pathology in Captan Long-Term Feeding Studies - Rats

NCI - Osborne Mendel Rats (NCI,1977)

Dose in ppm		0	6000	16000
Adrenal Cortical adenoma or carcinoma	(F)	0/64	2/50	3/47
	(M)	0/65	0/47	1/47
Thyroid C-cell adenoma	(F)	1/66	1/49	4/44
	(M)	2/65	1/42	1/47

IRDC - Charles River, CD Male Rat (RS) (Stauffer/Chevron, 1982)

Dose in ppm	0	25	100	250
Kidney Cortical Cell and/or Tubular Cell Tumors in Males				
Ademomas	1	0	2	3
Carcinomas	0	1	1	1
Totals	1/70	1/70	3/70	4/70

Table 9 shows the total number of animals with tumors of the glandular cells of the gastrointestinal tract, as recommended by the Board of Scientific Counselors, National Toxicology Program, in Appendix V of their report, "Report of the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation," August 17, 1984 (NTP, 1984).

The Agency notes that the tumor response is more significant at the 6000 ppm dose for the Socal high-dose study than in the Bio/Dynamics low-dose study. This may reflect a marked difference in the dosing schedules of the two studies. Nevertheless, the low-dose study demonstrates a significant increase in the same rare gastrointestinal tumors.

Table 9 - Summary of Pathology in Captan Long-Term Feeding Studies - Mice

Dose in ppm		0	100	400	800	6,000	10,000	16,000
NCI - B6C3FI Mouse (NCI, 1977)								
Duodenum								
Adenocarcinoma	(F)	0/68	-	-	-	0/49	-	3/48
	(M)	0/68	-	-	-	1/43	-	3/46
Socal High-Dose Study CD-1 Mouse (Chevron, 1982a)								
Adenoma or adeno-carcinoma of gastrointestinal tract	(F)	3/80	-	-	-	26/80	21/80	29/80
	(M)	3/80	-	-	-	19/80	22/79	39/80
Low-Dose Study, CD-1 Mouse (Bio/Dynamics, 1983)								
Adenoma/polyp or carcinoma of the gastrointestinal tract	(F)	0/100	1/100	3/100	3/100	7/100	-	-
	(M)	0/100	6/100	1/100	1/100	5/100	-	-

f. Human Studies

The Agency is unaware of any human studies that have investigated the oncogenicity of captan.

g. Weight-of-the-Evidence

The goal of the Hazard Identification step of the Cancer Risk Assessment is to reach a qualitative judgement on the evidence that captan may be a human carcinogen.

The data show that captan has demonstrated statistically and biologically significant oncogenic responses in both sexes of mice and in male rats. Tumors, including adenocarcinomas, of the digestive tract were observed in both sexes of mice in three studies. Although negative results were reported for Sprague Dawley rats in a 2-year study submitted by Makhteshim Chemical Works, Ltd. Beer-Sheva, Israel (1983), kidney tumors were observed in Charles River CD male rats in the IRDC study

As further supporting evidence, captan is structurally similar to folpet and captafol which have demonstrated oncogenic effects in laboratory animals. Of primary importance, folpet has induced intestinal tumors, including adenocarcinomas in mice (Chevron, 1978 and 1982a). Captan also induces intestinal adenocarcinomas in mice; this type of tumor is quite rare in rodents. Captafol produced a dose-related increased incidence

of fibroadenomas of the mammary gland and an increased incidence of neoplastic nodules in the liver of the female rat and lymphosarcomas, myeloproliferative disease, and hemangiosarcomas in both sexes of mice (Chevron, 1982). However, as these tumors were not seen in captan treated mice, they are not as significant as the intestinal adenocarcinomas induced by folpet.

As discussed in detail above, in section II.C.1.d., captan has been demonstrated to be mutagenic in microbial systems and in in vitro cell assays. Captan produced chromosome aberrations in cultured (in vitro) human embryo lung cells, kangaroo rat cells and in Chinese hamster ovary V79 cells. In general, captan produced these mutagenic events only in the studies lacking a metabolic activation system. When a metobolic activation system was included the mutagenic activity of captan was greatly reduced or undetectable. Captan is either non-mutagenic in in vivo assays or possesses a low mutagenic capacity. The in vitro tests as performed using captan present many more target sites for potential mutation detection than do the in vivo tests. In addition, the cells examined for mutagenic effects in the in vivo tests are not those in which oncogenic effects were seen. For these reasons, the lack of detectable mutagenic effects in the in vivo assays does not preclude the possibility that captan may be genotoxic and may induce tumors, particularly at the initial site of metabolism in the intestines.

The Agency concludes that captan is a demonstrated animal oncogen. There are no data available concerning direct evidence of oncogenic effects in humans. Therefore, the Agency takes the position that captan should be viewed as having the potential to be a human oncogen. In the context of the categorization adopted by the Agency's modification of the International Agency for Research on Cancer (IARC) classification scheme (U.S. EPA, 1984), captan has been assigned to category B2, a probable human carcinogen.

2. Dose Response Assessment

The analysis of the rat data focuses on kidney adenomas and carcinomas while the corresponding work for mice also counts adenomas and adenocarcinomas of the stomach, duodenum, and jejunum-ileum. The rationale for combining these organ sites and tumor types in the mouse studies is outlined in the National Toxicology Program - Board of Scientific Councillors Meeting, September 23 and 24, 1982 (NTP, 1982).

The tumor data are summarized in Table 8. Statistically significant increases in adenomas (benign) and adenocarcinomas (malignant) of the gastrointestinal tract of male and female mice and kidney tumors in male rats were found.

The Agency has used the linearized Multi-Stage model for risk assessment purposes for the reasons discussed in the Agency's Proposed Guidelines (U.S. EPA, 1984, 49 FR 46294).

There is currently no compelling biological rationale for using any particular model. The Multi-Stage model provides a consistently adequate fit to both male and female tumor data and it appears to be the most stable estimator. The Multi-Stage model is stable with respect to the data in that minor changes in the input data cause little or no change in model parameters such as Q_1^*(potency). Consider the following potencies (Q_1^*):

male mice HDS	3.9×10^{-3} $(mg/kg/day)^{-1}$
male mice LDS	1.0×10^{-3} $(mg/kg/day)^{-1}$
female mice HDS	3.4×10^{-3} $(mg/kg/day)^{-1}$
female mice LDS	2.0×10^{-3} $(mg/kg/day)^{-1}$
male rats	2.4×10^{-3} $(mg/kg/day)^{-1}$

All of the Q_1^* values are tightly grouped. Assuming that the distribution of the Q_1^* is a positive random variable but is otherwise unknown, and if the tight grouping of the Q_1^*'s is indicative of the true value, then a reasonable way to pool the values is to estimate an overall Q_1^* by the geometric mean. This gives the value of $Q_1^* = 2.3 \times 10^{-3}$ $(mg/kg/day)^{-1}$.

The estimates of Q_1^* presented above represent the upper 95% bound on the Q_1^*. The lower limit of the Q_1^* approaches zero.

3. Exposure Analysis

Captan (N-trichloromethylthio-4-cyclohexene-1,2-dicarbimide) is a fungicide registered for use to control a wide variety of fungal diseases on fruit, vegetable, field and ornamental crops; seeds; wooden packing house boxes; in soils; walls of homes; cosmetics; pharmaceuticals; oil based paints; lacquers; paper; wallpaper paste; plasticizers, polyethylene; vinyl; rubber; textiles; and in combination with insecticides on crops, seeds, and household pets. Captan is formulated as wettable powders, flowables, dusts, and granules. It is an ingredient in approximately 600 pesticide products registered in the United States. The entire U.S. population may be exposed to captan residues through the diet from eating food crops which have been treated with captan.

a. Agricultural Uses

(1) Applicators and Mixer/Loaders

When work on the captan PD 2/3 began, the Agency limited the non-dietary exposure analysis to 7 representative use sites. The sites included apples, strawberries, home gardens, almonds, apples, potatoes, and soybeans. These sites were chosen because one or more of the following criteria applied: (1) a high volume use; (2) a high percent of crop treated; (3) availability of a good captan exposure study or surrogate study; and (4) the potential for high exposure.

The Agency determined that these estimated risks were high enough to merit looking at all sites to see if the risks from these remaining sites were in the same order of magnitude, higher, or possibly lower. The results are summarized in Tables 10 and 11.

A discussion of the assumptions used to estimate non-dietary exposure and a discussion of the results follow (Day, 1984a and Jensen, 1982).

(1) FRUIT CROPS - FOLIAGE AND PRE-HARVEST USES

Generally captan is applied as a 50% wettable powder (WP) to fruit crops. Low- or high-volume ground air-blast equipment is used. From 2 to 15 applications are made per year, with mixing/loading and application taking from 4.0 to 6.5 hours at approximately 7 day intervals.

For certain application methods, the Agency has an extensive data base available for use in estimating applicator exposure. In such instances, the Agency's policy is to use this generic data base for exposure assessments rather than the results of individual studies conducted with a limited number of replicates (Reinert and Severn, 1985).

Table 10 - Non-Dietary Exposure Estimates for Mixer/Loaders

Fruit Crops	AI/A. Rate	Hrs Day	Hrs. Yr.	Max. Appl. Number Season	Exposure in mg Hourly Dermal	Hourly Inhalation	Yearly Dermal	Yearly Inhalation
Almonds[1/]	-	-	-	-	800[1/]	3.2[1/]	1600	6.4
Apples (pre-harvest)	3	0.5	5	10	180	6	900	30
Apples (post-harvest)	-	0.25	7.5	30	180	6	1100	45
Apricots	4	0.5	2	4	180	6	360	12
Avocado	4	0.5	2	4	180	6	360	12
Blackberry	1	0.5	2.5	5	180	6	450	15
Blueberry	1	0.5	5	10	180	6	900	30
Cherries	4	0.5	5	10	180	6	900	30
Citrus	4	0.5	1	2	180	6	180	6
Cranberry	4	0.5	1.5	3	180	6	270	9
Grapes	1.5	0.5	3	6	180	6	540	18
Mangos	5	0.5	6	12	180	6	1100	36
Nectarine	5	0.5	2.5	5	180	6	450	15
Peaches	5	0.5	2.5	5	180	6	450	15
Pears	2.5	0.5	3	4	180	6	540	18
Plum	3	0.5	3.5	7	180	6	630	21
Pineapple	2	0.5	13	26	180	6	2300	78
Vegetable Crops								
Beans	2.5	0.5	4	8	180	6	720	24
Beets	2.5	0.5	3.5	7	180	6	630	21
Carrots	2.5	0.5	4	8	180	6	720	24
Celery	5	0.5	6.5	13	180	6	1200	39
Curcurbits	2	0.5	6.5	13	180	6	1200	39
Eggplant	2	0.5	7	14	180	6	1300	42
Lettuce	2.5	0.5	4	8	180	6	720	24
Peppers	2.5	0.5	10	20	180	6	1800	60
Potatoes (foliar)	4	0.5	8.5	17	180	6	1500	51

Table 10 (continued)

	AI/A. Rate	Hrs Day	Hrs. Yr.	Max. Appl. Number Season	Exposure in mg Daily Dermal	Daily Inhalation	Yearly Dermal	Yearly Inhalation
Potatoes (seed treatment)	-	0.44	2.2	5	8	1	41	3.5
Rhubarb	4	0.5	5	10	180	6	900	30
Soybeans (seed treatment)	-	0.25	0.5	2	8	1	19	2
Spinach	4	0.5	2	4	180	6	360	12
Sweetcorn	4	0.5	5	10	180	6	900	30
Tomatoes	4	0.5	6.5	13	180	6	1200	39
Ornamentals								
Azaleas	2	0.5	2	4	180	6	360	12
Begonias	2	0.5	6	12	180	6	1100	36
Carnations	2	0.5	10	20	180	6	1800	60
Mums	2	0.5	10	20	180	6	1800	60
Diconda(CA)	2	0.5	1.5	3	180	6	270	9
Turf	2	0.5	10	20	180	6	1800	60
Roses	2	0.5	10	20	180	6	1800	60
Flowers	2	0.5	7.5	15	180	6	1400	45

1/ Assumes 800 lbs captan/day are loaded and average dermal and respiratory exposure are 1 mg and 0.004 mg per lb of captan loaded.

Table 11 - Non-Dietary Exposure Estimates for Applicators

Fruit Crops	AI/A. Rate	Hrs Day	Hrs. Yr.	Max. Appl. Season	(1) Appl. Mode	Exposure in mg Hourly Dermal	Hourly Inhalation	Yearly Dermal	Yearly Inhalation
Almonds	2.5-6	4	8	2	A	2.27	neg.	18	neg.
Apples	3	6	60	10	AB	30	0.06	1800	1
Apricots	4	6	24	4	AB	35	0.06	840	1
Avocado	4	6	24	4	AB	35	0.06	840	1
Blackberry	1	6	30	5	GB	24	0.06	720	2
Blueberry	1	6	60	10	GB	24	0.06	1440	4
Cherries	4	6	60	10	AB	35	0.06	2100	4
Citrus	4	6	12	2	AB	35	0.06	420	1
Cranberry	4	6	18	3	GB	24	0.06	430	1
Grapes	1.5	6	36	6	GB	24	0.06	860	2
Mangos	5	6	72	12	AB	40	0.06	2900	4
Nectarine	5	6	30	5	AB	40	0.06	1200	2
Peaches	5	6	30	5	AB	40	0.06	1200	2
Pears	2.5	6	24	4	AB	28	0.06	670	2
Plum	3	6	42	7	AB	30	0.06	1300	3
Pineapple	2	6	156	26	GB	24	0.06	3740	9
Vegetable Crops									
Beans	2.5	6	48	8	GB	24	0.06	1150	3
Beets	2.5	6	42	7	GB	24	0.06	1000	3
Carrots	2.5	6	48	8	GB	24	0.06	1150	3
Celery	5	6	78	13	GB	24	0.06	1870	5
Cucurbits	2	6	78	13	GB	24	0.06	1870	5
Eggplant	2	6	84	14	GB	24	0.06	2000	5
Lettuce	2.5	6	48	8	GB	24	0.06	1150	3
Peppers	2.5	6	120	20	GB	24	0.06	2900	7
Potatoes (foliar)	4	6	102	17	GB	24	0.06	2400	6
Potatoes (seed treatment)	-	5.6	33	5	-	0.35	0.03	10	1
Rhubarb	4	6	60	10	HS	1.7	0.0017	100	0.1
Spinach	4	6	24	4	GB	24	0.06	580	1
Strawberries	3	1	10	10	GB	24	0.06	240	1

Table 11 (continued)

	AI/A. Rate	Hrs Day	Hrs. Yr.	Max. Appl. Season	(1) Appl. Mode	Exposure in mg (1) Hourly Dermal	Hourly Inhalation	Yearly Dermal	Yearly Inhalation
Sweetcorn	4	6	60	10	GB	24	0.06	1440	4
Tomatoes	4	6	78	13	GB	24	0.06	1870	5
Homegardens	-	1.2	5	4	HS	1.7	0.0017	8	0.008
Ornamentals									
Azaleas	2	6	24	4	GB	24	0.06	580	1
Begonias	2	6	72	12	GB	24	0.06	1700	4
Carnations	2	6	120	20	GB	24	0.06	2980	7
Mums	2	6	120	20	GB	24	0.06	2900	7
Diconda(CA)	2	6	18	3	GB	24	0.06	430	1
Turf	2	6	120	20	GB	24	0.06	2980	7
Roses	2	6	120	20	GB	24	0.06	2900	7
Flowers	2	6	90	15	GB	24	0.06	2200	5

(1) The following exposure values by method are:

Method	Abbreviation	Dermal mg/hr	Respiratory mg/hr	Reference
airblast	AB	4.8 (Rate)+ 16	0.06	Reinert and Severn, 1985 Stauffer, 1982a
ground	GB	24	0.06	Stauffer, 1982a and Reinert and Severn, 1985
handspray	HS	1.7	0.0017	Jensen, 1982
aerial	A	2.27	neg.	Jensen, 1982

The most extensive exposure data base the Agency has is for the application of pesticides to orchards using high pressure or airblast equipment. This data base was used to estimate captan exposure to applicators, rather than the two studies which have been conducted with captan (Stauffer, 1982; and Deer, 1981). While the exposures shown in the Stauffer and Deer studies were in the same range as the Agency's data base, the Agency believes that its data base is more scientifically reliable. Mixer/loader data from the Stauffer study were used, however, because the Agency does not possess an extensive generic data base on mixer/loaders.

The orchard airblast data base consists of 23 nonproprietary studies containing more than 1,000 exposure replicates. A linear regression analysis of dermal exposure as a function of application rate revealed a valid predictive correlation which was statistically significant at the <0.01 level. The linear regression lines fit the equation $y = 4.8 x + 16$, where "y" is the dermal exposure in mg/hr (normalized to 3,000 cm^2 of exposed skin, i.e. long pants, short-sleeved shirt, no hat or gloves) and "x" is the application rate in lb. a.i./acre. From this data base, dermal exposure to applicators (assuming 2 lb a.i./acre) would be 26 mg/hr.

Inhalation exposure for airblast applicators does not correlate well with application rate. For the 23 studies, the mean inhalation exposure was 0.06 mg/hr (Day, 1982).

For mixer/loaders, the Stauffer study showed dermal and respiratory exposure of 180 and 6 mg/hr, respectively.

The Agency used the following assumptions to estimate worker exposure:

1. The worker does not wear special protective clothing such as a hat or gloves. The worker wears a short-sleeved, open-neck shirt, and long pants.

2. For a typical case there are 2 to 12 spray operations, with each operation lasting approximately 6 hours.

3. The mixing/loading operation takes 0.5 hours.

(2) VEGETABLE CROPS AND ORNAMENTALS - FOLIAGE AND PRE-HARVEST USES

Generally vegetable and ornamental crops are treated with captan using a tractor-mounted row-crop low-boom sprayer. Growers with smaller acreages might use hand-held applicators. A 50% WP is used most often at a rate of 2 to 5 pounds a.i. per acre.

Because no captan row-crop exposure study was available to the Agency, surrogate data were used.

The data base used to assess dermal exposure for ground boom applicators was on the results of a series of studies sponsored by the Agency and carried out at various state universities under the National Pesticide Hazard Assessment Program. The full report of these studies is currently undergoing formal Agency Peer Review, but a summary of the studies has been published (Reinert and Severn, 1985).

The Agency used the Stauffer airblast study to assess inhalation exposure for applicators and mixer/loaders and dermal exposure for mixer/loaders.

For dermal exposure, the Agency estimates 180 mg/hr for mixer/loaders (Stauffer, 1982a) and 24 mg/hr for applicators (Reinert and Severn, 1985).

For respiratory exposure, the Agency estimates 6 mg/hr for mixer/loaders and to 0.06 mg/hr for applicators (Stauffer, 1982).

The Agency used the following assumptions to estimate worker exposure:

1. The worker does not wear special protective clothing such as a hat or gloves. The worker wears a short-sleeved, open-necked shirt, and long pants.

2. There are 4 to 20 applications per year. Each application lasts an average of 6 hours. This is a worst-case estimate.

3. The mixing/loading operation takes 0.5 hours.

(3) HOME GARDENS - FOLIAGE AND PRE-HARVEST USES

For home garden use, 90 percent of captan is applied to fruit trees (Pelletier, 1982a). Other uses include vegetable gardens, ornamental flowering plants, lawns, and dicondra ground covers. A variety of equipment (hose-end sprayers, atomizer spray bottles, pump-up sprayers, dusters, etc.) is used. Generally, a 50% WP is used at a rate of 0.8 oz a.i. in 5 gallons of water, although granular and captan WP formulations with less active ingredient are available.

The range of application exposure times depend on such parameters as the crop treated, geographic location, size of garden, and can widely vary. No data are available for estimating a reasonable minimum value. However, as an estimate for a home gardener using captan with a small vegetable garden, the Agency assumes for a minimum value that the gardener will take 20 minutes, twice a year.

The Agency used the following assumptions to estimate worker exposure:

1. The home gardner does not wear special protective clothing such as a hat or gloves. A home gardener wears a short-sleeved, open-necked shirt, and long pants.

2. No published captan exposure studies were available. Although the Agency has several home gardener studies on surrogate chemicals, the use patterns for these studies were for application to low crops such as vegetable gardens and to ornamentals. A model (Lavy et al. 1980) which represents the anticipated upper body exposure during fruit tree application more accurately was chosen. In the study, the herbicide 2,4,5-T (1.9%) was applied by backpack sprayer during typical forestry operations. The average dermal and respiratory exposures found were 26.7 and 0.027 mg/hr, respectively. Corrected for concentration differences between captan (0.12%) and 2,4,5-T (1.9%), the equivalent captan values would be 1.7 mg/hr dermal exposure and and 0.0017 mg/hr respiratory exposure.

3. The average home gardener applying captan would have 4 fruit trees. The Agency estimates that it would take 1.25 hours to mix and spray captan on these trees, and that 4 applications are made at least at seven-day intervals per year (Pelletier, 1982a).

Assuming 1.7 mg/hr exposure to captan for 1.2 hr/application, a reasonable estimate of the dermal exposure would be 2.0 mg/day (or 8 mg/yr).

For the respiratory exposure, a reasonable estimate of the exposure to captan would be 0.002 mg/day (or 0.008 mg/year).

(4) NUT CROPS (ALMONDS)

Captan is applied primarily as a 50% WP using ground air-blast equipment, however, aerial equipment may be used in emergency situations when extended periods of rain prevent use of ground equipment. Since data for captan exposure using aerial equipment were not available, surrogate data were used to estimate worker exposure. An 80% captan WP formulation is commonly used for aerial applications, at a rate of from 2.5 to 6 lbs a.i. per 15 to 30 gallons of water.

The Agency estimates that an average almond orchard is 52 acres, and that it would take up to 3 tankfuls per application day to cover such a farm. However, aerial application is usually done by commercial applicators who would be applying captan to more than one farm. Because the almond orchards are in a rather concentrated geographic area and aerial appli-

cations are done during emergency situations, the timing of application is critical. Therefore, it is estimated that an aerial application crew would be working for a two-day period for 3 applications, at 7 to 10 day intervals.

It is standard procedure that the chemical is pumped via a closed system into the spray tanks after mixing.

The Agency used the following assumptions to estimate exposure for mixer/loaders and pilots:

1. A mixer/loader and pilot wear a short-sleeved, open-necked shirt, and long pants.

2. For estimating exposure to aerial mixer/loaders, no captan study was available to the Agency. A surrogate study (Everhart and Holt, 1982) using Benlate® (50% benomyl WP) during the mixing/loading was available. In this study, the average dermal and respiratory exposures were 1 mg and 0.004 mg, respectively, per pound of active ingredient loaded. Five hundred lbs. of Benlate® were assumed loaded per application day.

3 The Agency assumes that once a year a mixer/loader loads 800 lbs. of captan per day for a two-day period.

4. For evaluating exposure to pilots, a pilot would be exposed for 4 hours each day, for a two-day application period. It is assumed, based on estimates made for pilots spraying EBDC's, that pilots are exposed dermally to 2.27 mg/hr (Jensen, 1982). No significant respiratory exposure was found.

For the mixer/loaders, the Agency estimates a daily dermal exposure of 800 mg/day (or 1600 mg/year) and a respiratory exposure of 3.2 mg/day (or 6.4 mg/year). The range is based on the use from one to 3 applications per year. Therefore, the high end of the annual exposure range is three times these dermal and respiratory exposure values. One application lasting two days is considered the minimum of the range. These values represent exposure potential when no special protective clothing is worn.

For the pilots not involved with any mixing/loading tasks, the Agency estimates a daily dermal exposure of 9 mg/day (or 18 mg/year) and negligible respiratory exposure.

(5) APPLES - POST-HARVEST USES

Captan is used mostly in the Northeast U.S. as a post-harvest treatment to prevent apples from rotting during storage. After harvest, apples contained in wooden bins are mechanically dipped or sprayed with 0.1% captan suspension. In the case of the spray treatment method, the excess captan is recycled.

After treatment, the apples are stored or sorted, washed, waxed, and dried prior to shipment.

Two workers per storage/packing house could potentially be exposed to captan. One may mix and control the captan suspension, and one may oversee the apples being conveyed into and out of the dip or drench area. Spraying or dipping operations are automated. The worker who prepares the captan suspension, however, is the one with the potential for significant exposure to captan. Because of captan's low vapor pressure and rapid hydrolysis rate, volatilization of captan from the diptank suspension is considered negligible.

A worker in this situation would likely be wearing a long-sleeved shirt and perhaps a hat because of the prevailing autumn weather conditions; therefore, for this analysis, only hand exposure was considered.

It is estimated that treatment periods range from 6 weeks in West Virginia (with a mixer working 5 minutes per day preparing one batch of dip or spray suspension) to 12 weeks in Washington State (with a mixer working 20 minutes per day preparing the captan suspensions and adding captan to the tanks when the volumes of suspension are reduced) (Pelletier, 1982a).

The Agency made the following assumptions to estimate exposure:

1. A worker wears a long-sleeved shirt and long pants, but no gloves while mixing and maintaining the captan suspension for dipping and spraying.

2. No specific captan exposure model for this use was available to the Agency. It is the Agency's judgment, however, that the exposure to the mixer for this post-harvest use would be similar to the exposure found during the mixing portion of the apple pre-harvest exposure study (Stauffer, 1982a). In this study, the mixer/loader was exposed dermally to 153 mg/hr on the hands and 28 mg/hr on the remainder of the exposed skin area. Respiratory exposure was 5.9 mg/hr, assuming a 1.2 m^3/hr breathing rate.

3. A typical case as in West Virginia results in 15 minutes mixing per day (3 batches) over a six-week period, or a total of 7.5 hours per year of exposure.

For the worker who mixes the captan suspensions for this post-harvest use, the Agency estimates a dermal exposure of 38.3 mg/day (or 1100 per year) and a respiratory exposure of 1.5 mg/day (or 45 mg/year).

For the range, a minimum value is derived from a 5 minute per day mixing period for 6 weeks (2.5 hours total), which would be reasonable for West Virginia. A maximum value is derived from the practice in Washington State, where mixing times would likely be 20 minutes per day over an 8-month period (53 hours total exposure). The range of dermal exposure, would be from 13 mg/day (or 390 mg/year) to 51 mg/day (or 8,200 mg/yr). The respiratory exposures would likely range from 0.5 mg/day (or 15 mg/year) to 2 mg/day (or 320 mg/year).

(6) POTATOES - PLANTING STOCK TREATMENT USES

In the early spring seed potatoes are generally cut by a potato-cutting machine (usually located indoors). The cut surfaces of the potato seed pieces are then dusted with captan by means of a duster mounted on a conveyer belt. The captan treated potato seed pieces are then distributed by a movable conveyer belt into the hoppers of a tractor-driver planter.

Four dust formulations (ranging in concentration from 5 to 22.5% percent a.i.) and a 50% WP are registered for treatment of potato seed pieces at a rate of 0.5 lb a.i. per 100 lb of potato seed pieces.

There is a wide variety of application practices for this use. In Maine, the average farm is about 90 acres. Sufficient seed pieces for one day's planting are treated with captan on the planting day. Two workers are involved in the treatment operation. One fills captan into the treater and oversees the mechanical cutting operation. The other unloads and loads seed material before and after treatment. The Agency estimates the exposure time would be 2.2 hrs for filling, 44 hrs for cutting, and 45 hrs for planting (Pelletier, 1982a). One worker would also plant the seed material and the other would haul treated seed fertilizer, and load the planter boxes.

In Idaho, the farms are an estimated 300 acres. Four to 5 workers are involved in the seed treatment operation. The operation is carried out for an eight-hour day over a 2 to 3 week period. Assuming a 3 week exposure period, the exposure times would be 7.2 hrs for filling, 44 hrs for cutting, and 45 hrs for planting.

Potato planting usually takes place in areas of the northern United States in the early spring, which is normally quite cool. Workers are nearly always fully clothed with head coverings and long-sleeved shirts or jackets. For this reason, no potential dermal exposure is estimated in this analysis for areas other than the face, neck, and hands.

The Agency used the following assumptions to estimate worker exposure:

1. The potential dermal and respiratory exposures reported in the study by E. R. Stevens and J. E. Davis are representative of potato seed piece treatment across the U.S. (Stevens and Davis, 1980). A 5% captan dust formulation was used. The potential exposures varied considerably with work task and is summarized in Table 12.

2. The use practices and exposure durations described for Maine are typical for most of the U.S., and the practices in Idaho represent the upper end of the range of exposures for potato seed piece treatment.

3. Only the hands, face, and neck are not covered by protective clothing.

4. In Maine, the total seed piece treatment/planting operation is estimated to take 5 consecutive days, once a year. Broken down on a daily basis involving two people, person number one needs 0.44 hrs for filling and 8.8 hrs for cutting; and person number two needs 5.6 hrs for planting.

5. Because exposure estimates vary with the task involved, the Agency assumes that one person does the filling and cutting, and the other does the planting.

Table 12 -- Potential Exposure of Workers to Captan During Potato Seed Piece Treatment

Operation	Average Dermal Exposure not including hands[1/] (mg/hr)	Average Hand Exposure (mg/hr)	Average Dermal Exposure (mg/hr)	Average Respiratory Exposure (mg/hr)
Filling Duster	4.12	3.56	7.68	0.82
Cutting/Sorting Pieces	0.55	N/A[2]	0.55	0.04
Planting Pieces	0.33	0.02	0.35	0.03

[1/]Because potato seed piece treatment is done in early spring, which is usually quite cool, workers were clothed with head coverings and long-sleeved shirts or jackets. Therefore, dermal exposure is estimated only for face, neck, and hands.

[2/]Hand exposure is not included in the data because workers on the cutting machine always wore rubber gloves.

For a person doing the filling and cutting, the daily dermal and respiratory exposures are estimated to be 8.2 mg/day (for example, 0.44 hrs x 7.68 mg/hr + 8.8 hrs x 0.55 mg/hr) and 0.7 mg/day, respectively. For the person doing the planting, the dermal and respiratory exposures are estimated to be 2.0 mg/day and 0.2 mg/day, respectively. This exposure level would be maintained for 5 consecutive days, once a year.

The minimum end of the actual use range can be estimated based on a small potato farm of approximately 10 acres. Although the daily exposures would likely be the same (i.e., 8.2 and 0.7 mg/day for dermal and respiratory exposures, respectively), it is estimated that workers would be exposed for no more than 2 consecutive days per year.

The maximum end of the range for this use can be found by extending these exposures to fifteen consecutive days. This would be applicable in Idaho, where farmers have larger acreages available for planting with potatoes. The daily exposures for a person doing the cutting and filling would be still be 8.2 mg/day and 0.7 mg/day for dermal and respiratory, respectively, but extending for 15 consecutive days per year.

(7) SOYBEANS - PLANTER BOX SEED TREATMENT USES

Seed can be treated in large, bulk seed quantities by commercial seed companies; in smaller bulk quantities on the farm before planting; or in planter boxes at the time of planting. The planter box method is most common because of its convenience, and because it preserves the farmers' options of diverting untreated seed for use as animal feed.

There are 2 types of planter box treatments. The first is called the mechanized planter box method. A simple powder metering device is located at the intake of the auger used to transfer the seed from a bulk source to the planter. The second method, the one used for this analysis, is the so-called manual planter box method. With this method, captan plus other fungicides and/or insecticides are added by means of a container or scoop to the seeds already in the planter box, then mixed manually or by gravity/filtration.

Captan is used as a seed treatment on many different types of seed. It is reported that 96% of the corn seed treatments are accomplished commercially and the remainder are treated by individual growers (Pelletier, 1982a). Soybeans, however, were chosen as the representative crop for this analysis because a large percentage of the soybeans treated with captan are treated by using the manual planter box method. The Agency assumes this treatment practice has higher potential for applicator/ farmer exposure than the commercial practice.

Commercially treated seed and seed augered into hoppers produce some (albeit less) dust exposure than by the manual

planter box method (Zoecon's Lindane PD 2/3 Rebuttal Submission, 1980.)

Captan is formulated by itself or as a mixture with other pesticides (such as diazinon, lindane, maneb, and methoxychlor) to prevent a number of soil and seed borne diseases. Twenty-five percent dusts are most commonly used, although dusts from 6% to 75% are available.

The average number of acres being planted with captan-treated soybean seeds ranges from 29 to 100 (Pelletier, 1982a). It is estimated to take less than 1/4 hour for treating and loading seed per 10 hour work day, with approximately 90 acres treated in that time period (Zoecon's Lindane PD 2/3 Rebuttal Submission, 1980). For estimating the range of exposures, the minimum was based on a single exposure day (which would be reasonable for a small soybean farm) and the maximum based on 3 days of exposure (which would be reasonable for a large soybean farm). Both values assume a 0.25 hr/day for seed treatment and hopper filling, and 7 hrs/day for seed planting.

The Agency used the following assumptions to estimate exposure:

1. A 25% dust formulation is used.

2. Since no actual captan planter box exposure study was available to the Agency, it is reasonable to use the exposure values found in the captan potato seed piece study (Stevens and Davis, 1980). For a 5% dust formulation, the average dermal and respiratory values found while filling the duster were 7.68 and 0.82 mg/hr, respectively. Corrected for the use of a 25% dust formulation, exposure values of 38 and 4 mg/hr will be used for the combined operations of seed treatment and hopper fill.

3. No protective clothing was assumed. A farmer treating seed using captan using the manual planter box method is assumed to be wearing a short-sleeved, open-necked shirt, long pants, no gloves or hat.

4. Seed treatment and hopper fill take 0.25 hours per day, 2 days per year. Seed sowing takes two 7-hour days, or 14 hours per year (Zoecon's Lindane PD 2/3 Rebuttal Response, 1980; Pelletier, 1982a).

5. Compared to seed treatment and hopper fill, the Agency assumes that the exposures are negligible for the actual seed planting operation.

For seed treatment and hopper fill (the same person would likely do both operations), the dermal and respiratory exposures

are estimated to be 9.5 mg/day (or 19 mg/year) and 1 mg/day (or 2 mg/year), respectively.

For seed treatment the dermal and respiratory exposures are assumed to be negligible compared to the exposures while treating seed and filling the hopper.

2) Harvesters (Fieldworkers)

There are 7 available studies of fieldworker exposure to captan applied to strawberries. See Table 13 for detail of the data from these studies and calculations of yearly exposure (Adams, 1984).

One of the studies was performed in Oregon where school-age children are usually employed as pickers for about six weeks per season with 30 days of exposure per year (Popendorf, 1984). The children may only work for one season or less, and rarely work in the strawberry harvest for more than 3 years. The strawberry picker exposure rate of 4.70 mg/hr for the Oregon study was the lowest rate in the 7 studies. Estimated lifetime captan exposure derived from this study is 3.39 grams for strawberry pickers in Oregon.

Six of the studies were performed in California where harvesting is usually done by residents of the area, and the harvest may last for 80 work-days. In this case, people may work in strawberry agriculture for as many as 20 years (Popendorf, 1984). One of these studies included exposure to weeders as well as pickers. In that case, exposure to weeders, at 94.13 mg/hr, was much higher than to pickers, at 17.41 mg/hr. However, the weeding of strawberries is performed only about 10 days/season.

The 6 California picker-exposure values range from 3.76 to 24.97 g/yr with a mean of 9.85 g/hr. Based on the mean of these measured values, lifetime exposure (20 years) for a person only picking strawberries would be 197.0 g/lifetime. The exposure for a California worker only engaged in weeding strawberries, would be 150.6 g/lifetime. Combination of the 2 tasks (10 days of weeding and 70 days of picking per year) could lead to the largest lifetime exposure, [(9.85 g/yr) (70/80) + 7.53 g/yr] (20) = 323.0 g/lifetime.

Strawberry pickers and perhaps weeders have the opportunity to eat the fruit. That fruit is reported to average 0.62 ppm (SD = 0.052) from 7 sets of residue data, whose means range from undetectable to 1.20 ppm (Popendorf et al. 1982). Assuming that the workers eat a daily average of 430 g [(1 pint) (454 g/pint) (0.95 g/g density) = 430 g], a worker would ingest 0.00052 g/day [(430 g) (1.2×10^{-6} g/g) = 0.00052 g/day] of captan residues with the fruit. Addition of this ingestion exposure to the exposures above increases the estimated lifetime exposures. The estimated lifetime exposures are: 3.44 g for Oregon Pickers (0.00052 g/d) (30 d/yr) (3 yr) + 3.39 g]; 197.3

Table 13 - Estimation of Fieldworker Exposure to Captan on Strawberries

Study No.	State	Task	Days after application	Non-ingestion Exposure				References
				mg/hr	hr/d	d/yr	g/yr	
1.	Calif	Picking	10	6.50	8	80	4.16	Popendorf et al. 1982
2.	Oreg	Picking	26	4.70	8	30	1.13	Popendorf et al. 1982
3.	Calif	Picking	3	17.41	8	80	11.14	Popendorf et al. 1982
"	Calif	Weeding	3	94.13	8	10	7.53	Popendorf et al. 1982
4.	Calif	Picking	3	16.37	8	80	10.48	Popendorf et al. 1982
5.	Calif	Picking	48	5.88	8	80	3.76	Popendorf et al. 1982
6.	Calif	Picking	4	39.01	8	80	24.97	Zweig et al. 1983
7.	Calif	Picking	3	7.15*	8	80	4.58	Winterlin et al. 1984

Mean for 6 Calif. picking studies: 15.38 mg/hr; 9.85 g/yr

* This has been corrected to include hand exposure.

g for California Pickers (0.00052 g/d) (80 d/yr) (20 yr) + 197.4 g]; 151.4 g for California Weeders (0.00052 g/d) (80 d/yr) (20 yr) + 150.6 g]; and 323.8 g for a combination of picking and weeding in California [(0.00052 g/d) (80 d/yr) (20 yr) + 323.0]. Ingestion exposure relative to total exposure is small, ranging from 1.4% in Oregon to 0.3% for combined picking and weeding in California. However, that exposure portion may be absorbed better than the dermal exposure.

3) Cut Flower Production

Captan is registered for use in controlling diseases in cut flower production. These flowers include carnations, chrysanthemums, snapdragons, etc. The use of captan on chrysanthemums was selected as being typical of flower production and use practices.

The Agency has made the following assumptions about use (Day, 1985, and Pelletier, 1985):

1) An average acreage of flower production is eight acres.

2) Continuous, but staggered production throughout the year such that there are 52 plantings per year.

3) Plants flower 3-5 months after planting.

4) Each plant covers a 36 square inch area.

5) Captan is applied at the early bloom stage for a six month period during the year.

Based on the above assumptions, spray treatment was calculated to be 27 minutes/week for six months. Total time spent cutting stems and boxing flowers would be 2.8 hours for 20-24 days over a six month period. This is summarized as follows:

Operation	Hours/Day	Days/Year	Hours/Year
Mix/load/cleanup	0.25	26	6.5
Spraying	0.5	26	13
Cutting/packing	2.8	132	370

The Agency estimates that the respiratory exposure for applicators and mixing and loading is 0.2 mg/hour and that the dermal exposure for these activities is 17.0 mg/hour (Jensen, 1982). For cutting and packaging of flowers, the Agency used surrogate data from a study on malathion by Wolfe et al. (1967) to estimate exposure: the dermal exposure was 3.9 mg/hour for the first day and 2.1 mg/hour two days after application. The respiratory exposure was essentially negligible (Day, 1985). The exposure

estimate for workers (70 kg) engaged in these activities is as follows:

Operations	Hrs/Day	Exposure Rate mg/hr		Exposure in mg			
		Dermal	Inhalation	Dermal Daily	Dermal Yearly	Inhalation Daily	Inhalation Yearly
Mix/load/ spray/cleanup	0.75	17	0.2	13	332	0.15	3.9
Cutting/ packaging	2.8	2	neg.	6	740	neg.	neg.

Thus, based on a 70 kg person with no protective clothing, the exposure to captan from the cut flower industry would be:

Operations	Exposure - mg/kg			
	Dermal		Inhalation	
	Daily	Yearly	Daily	Yearly
Mix/load/spray/ cleanup	0.19	4.7	0.002	0.06
Cutting/packaging	0.09	11	neg.	neg.

4) Dietary Exposure - Oncogenic Risk

To estimate dietary exposure of the U.S. population to captan, the Agency assumed food residues were at tolerance levels (theoretical maximum residue contribution or TMRC), a body weight of 60 kg, 100 percent of a crop is treated, and standard food factors (i.e., percent of a crop in the diet). These estimates represent the worst case dietary exposure because residues are assumed to be at the highest levels which are legally permissible on a crop. Although actual residues could be lower, adequate data were not available to allow such a determination. Table 14 summarizes these estimates.

Data on pesticide residues found in food in the market place were also evaluated. The following surveys provided this information.

(a) Stauffer Chemical Company Market Basket Surveys (fruits and processed fruit commodities only);

(b) Chevron Chemical Company Market Basket Surveys (fruits and processed fruit commodities only);

(c) Canadian residue data on imported commodities (fruits and vegetables); and

(d) FDA monitoring programs for 1978-1981 (fruits and vegetables).

Table 14 - Dietary "Worst Case" Exposure Based on Tolerances for Captan

Food Commodity or Commodity Grouping	Food Factor (percent diet)	Tolerance (ppm)	Daily Intake (mg/1.5kg diet/day)
Almonds	0.03	2.00	0.00090
Apples	2.53	25.00	0.94875
Apricots	0.11	50.00	0.08431
Avocados	0.03	25.00	0.01125
Beans	2.04	25.00	0.36500
Beet Greens	0.03	100.00	0.04500
Beets	0.17	2.00	0.00521
Blackberries	0.03	25.00	0.01125
Blueberries	0.03	25.00	0.01125
Broccoli	0.10	2.00	0.00307
Brussels sprouts	0.03	2.00	0.00090
Cabbage, sauerkraut	0.74	2.00	0.02207
Cantalopes	0.52	25.00	0.19545
Carrots	0.48	2.00	0.01441
Cattle	7.18	0.05	0.00539
Cauliflower	0.07	2.00	0.00215
Celery	0.29	50.00	0.21461
Cherries	0.10	100.00	0.15330
Collards	0.08	2.00	0.00246
Corn, sweet	1.43	2.00	0.04290
Cottonseed	0.15	2.00	0.00450
Crabapples	0.03	25.00	0.01125
Cranberries	0.03	25.00	0.01125
Cucumbers, pickles	0.73	25.00	0.27210
Dewberries	0.03	25.00	0.01125
Eggplant	0.03	25.00	0.01125
Garlic	0.03	25.00	0.01125
Grapefruit	0.99	25.00	0.37174
Grapes, raisins	0.49	50.00	0.36791
Hogs	3.43	0.05	0.00258
Honeydew melons	0.03	25.00	0.01125
Kale	0.03	2.00	0.00090
Leeks	0.03	50.00	0.02250
Lemons	0.17	25.00	0.06515
Lettuce	1.31	100.00	1.96219
Limes	0.17	25.00	0.06515
Mangoes	0.03	50.00	0.02250
Muskmelons	0.03	25.00	0.01125
Mustard Greens	0.06	2.00	0.00184

Table 14 (continued)

Food Commodity or Commodity Grouping	Food Factor (percent diet)	Tolerance (ppm)	Daily Intake (mg/1.5kg diet/day)
Nectarines	0.03	50.00	0.02250
Onions (dry bulbs)	0.72	25.00	0.26827
Onions, green	0.11	50.00	0.08431
Oranges	2.17	25.00	0.81247
Peaches	0.90	50.00	1.34900
Pears	0.26	25.00	0.09581
Peas	0.69	2.00	0.02085
Peppers	0.12	25.00	0.04599
Pimentos	0.03	25.00	0.01125
Pineapple	0.30	25.00	0.11114
Plums, Prunes	0.13	50.00	0.19928
Potatoes	5.43	25.00	2.03500
Pumpkin, Squash	0.11	25.00	0.04216
Quinces	0.03	25.00	0.01125
Raspberries	0.03	25.00	0.01125
Rhubarb	0.05	25.00	0.01916
Rutabagas	0.03	2.00	0.00090
Shallots	0.03	50.00	0.02250
Soybeans (oil)	0.92	2.00	0.02754
Spinach	0.05	100.00	0.07665
Strawberries	0.18	25.00	0.06898
Summer Squash	0.03	25.00	0.01125
Tangerines	0.03	25.00	0.01125
Taro	0.03	0.250	0.00011
Tomatoes	2.87	25.00	1.07805
Winter Squash	0.03	25.00	0.01125

However, the survey data that were submitted were not reliable enough to assess dietary exposure or to make a regulatory decision for the following reasons:

a) There may be a mixture of treated and untreated food in the survey, resulting in observed residues which are lower than tolerances.

b) There was no indication on the frequency of application or the amount of captan applied to the crops.

For informational purposes, exposure estimates using this information are presented in Table 15.

The seed treatment use of captan is now considered a food use. Although the Agency does not have data for residues in plants which might result from seed treatment, it is assuming, for the present, that the resulting residues would be at or below the limit of detection, and that based on those levels the dietary risks to humans would be insignificant. The Agency will be requesting residue data for seed treatments.

There are tolerances for detreated corn seed that is fed to cattle and hogs. This seed was previously treated with captan, but because it was not planted, the left over treated seed is detreated to remove captan from the seed. Based on feeding studies submitted by Chevron that showed that there would be no likely captan residues in these animals if a pre-slaughter interval of 14 days were adopted, no human dietary exposure is expected. A tolerance of 100 ppm was set (21 CFR 561.65).

5) Dietary Exposure - Teratogenic Risk

To estimate dietary exposure to captan for use in the teratogenic risk assessment, the Agency also used the tolerances and 60 kg average body weight. However, food factors were not used. Since one dose could cause an acute, teratogenic effect (as opposed to multiple doses causing a chronic, oncogenic effect), the Agency used "single serving" values (USDA, 1977). Table 16 summarizes the results.

b. Non-Agricultural Uses

The Agency has reviewed information related to some of the minor non-agricultural uses of captan (Day, 1984b). Captan is used in plastics, wallpaper flour adhesive, paints, cosmetics

Table 15 - Captan Dietary Exposure Based on Surveys

Food Commodity or Grouping	Food Factor (% diet)	Average of Actual Residues (ppm)	Daily Intake (ug/1.5 kg diet/day)
Almonds	0.03	0.003	0.0014
Apples			
Fresh	2.00	0.08	2.4000
Canned	0.32	0.007	0.0336
Juice	0.21	0.007	0.0347
Apricots	0.11	1.041	1.17177
Blackberries	0.03	0.078	0.0351
Blueberries	0.03	0.062	0.0279
Cherries (incl. canned)	0.10	0.39	0.585
Grapes			
Fresh	0.30	0.74	3.3300
Juice	0.15	0.006	0.0135
Raisins	0.04	0.011	0.0066
Lettuce	1.31	0.09	1.7685
Nectarines	0.03	0.053	0.0239
Oranges			
Fresh	1.35	0.000	0.0000
Frozen	0.40	0.017	0.1020
Juice	0.42	0.0115	0.0725
Peaches			
Fresh/Frozen	0.42	1.00	6.3000
Canned	0.48	0.017	0.1224
Pears (incl. canned)	0.26	0.03	0.1287
Plums, Prunes	0.13	0.012	0.0234
Raspberries	0.03	1.355	0.6098
Strawberries			
Fresh	0.15	1.67	3.7575
Frozen/Jam	0.03	0.071	0.0320
Tomatoes	2.87	0.07	3.0135

Table 16 - Captan Dietary "Single Serving" Exposure Estimate

Food Commodity or Grouping	Single Serving[1/] (Kg)	Tolerance (ppm)	Daily Intake (mg/day)
Almonds	Unknown	2.00	-
Apples	0.212	25.00	5.30
Apricots	0.114	50.00	5.70
Avocados	0.150	25.00	3.75
Beans, Lima, fresh	0.072	25.00	1.80
Bean, Snap, fresh	0.055	25.00	1.38
Beet Greens	0.076	100.00	7.60
Beets	0.080	2.00	0.16
Blackberries	0.072	25.00	1.80
Blueberries	0.072	25.00	1.80
Broccoli	0.092	25.00	0.18
Brussels sprouts	0.078	2.00	0.16
Cabbage, sauerkraut	0.090	2.00	0.18
Cantaloupes	0.160	25.00	4.00
Carrots	0.110	2.00	0.22
Cauliflower	0.115	2.00	0.23
Celery	0.120	50.00	3.00
Cherries	0.145	100.00	14.50
Collards	0.095	2.00	0.19
Corn, sweet	0.080	2.00	0.16
Cottonseed	unknown	2.00	-
Crabapples	unknown	25.00	-
Cranberries	0.070	25.00	1.75
Cucumbers, pickles	0.144	25.00	3.60
Dewberries	0.072	25.00	1.80
Eggplant	0.100	25.00	2.50
Garlic	0.003	25.00	0.08
Grapefruit	0.101	25.00	2.50
Grapes	0.080	50.00	4.00
Raisins	0.145	50.00	7.25
Honeydew Melons	0.170	25.00	4.25
Kale	0.055	2.00	0.11
Leeks	unknown	50.00	-
Lemons	0.016	25.00	0.40
Lettuce	0.057	100.00	5.70
Limes	0.016	25.00	0.40
Mangoes	0.082	50.00	4.10
Muskmelons	0.160	25.00	4.00
Mustard Greens	0.070	2.00	0.14
Nectarines	0.150	50.00	7.50
Onions (dry bulb)	0.171	25.00	4.28
Onions, green	0.025	50.00	1.25
Oranges, (juice)	0.245	25.00	6.12
Peaches	0.152	50.00	7.60
Pears	0.180	25.00	4.50
Peas (dried)	0.200	2.00	0.40
Peppers	0.100	25.00	2.50
Pimentos	0.018	25.00	0.45

Table 16 - continued

Food Commodity or Grouping	Single Serving[1/] (Kg)	Tolerance (ppm)	Daily Intake (mg/day)
Pineapple	0.084	25.00	2.10
Plums, Prunes	0.070	50.00	3.50
Potatoes	0.169	25.00	4.22
Pumpkin	0.245	25.00	6.12
Quinces	unknown	25.00	-
Raspberries	0.072	25.00	1.80
Rhubarb	0.122	25.00	3.05
Rutabagas	0.120	2.00	0.24
Shallots	0.010	50.00	0.50
Soybeans (curd)	0.120	2.00	0.24
Spinach	0.055	100.00	5.50
Squash (winter)	0.222	25.00	5.55
Strawberries	0.075	25.00	1.88
Summer Squash	0.120	25.00	3.00
Tangerines	0.100	25.00	2.50
Taro	unknown	0.25	-
Tomatoes	0.181	25.00	4.52
Turnips	0.130	2.00	0.26
Turnip Greens	0.072	2.00	0.14
Watermelon	0.160	25.00	4.00

1/ Source: USDA, 1977

and shampoos, surface sprays, pet powders, and packing crates to prevent fungal attack. These captan uses are somewhat specialized in that they are used to prevent fungal deterioration of organic substrates as opposed to use to prevent crop diseases.

In these uses, potential human exposure falls into two categories: (1) exposure to workers in adding captan formulations to inert products and (2) exposure to users of these end-use products treated with captan residues. Because of the difficulty in estimating exposure for specific uses for the formulations and the products themselves, the Agency has addressed only currently registered uses of captan and has made some general assumptions on the potential exposure to users only for likely exposure situations.

The relevant use situations were obtained from a Mitre Corporation Report (Mitre, 1981). This report is believed to represent the latest information on these non-agricultural uses of captan.

1) Plastics

Captan is used to inhibit fungal growth in plastic and rubber products. Though many of these polymers are inherently resistant to fungal attack, the additives, such as plasticizers, are not. Captan is added to protect these degradable additives and is particularly useful for the protection of products in warm, humid environments.

Use as an Additive

For these uses, EPA registered captan pesticide products containing 45-90% a.i. are employed. This powder formulation is added to vinyl, rubber, and polyethylene products at 0.5-3% w/w a.i. This use of captan in 1979 was 75,000 lbs. The use of captan has declined in recent years in favor of other products with more thermal stability, less UV sensitivity, and less tendency to discolor.

The primary products manufactured from these vinyl, rubber and polyethylene products containing captan as an additive are mattress covers, car vinyl tops, rubber gaskets, and vinyl coated fabrics. One use, for swimming pool liners, was discontinued when it was found that captan leached into the water. The current alternatives to captan are in general superior to captan in many respects and it is suggested that more effective and desirable alternatives exist. Because the toxicity data base for these chemicals is incomplete, some alternatives may be more, less, or equal to captan in toxicity. It is not possible to compare the toxicity of the alternatives to captan at the present time.

The Mitre report mentioned above describes a site visit to the only plant currently employing captan to make laminated vinyl fabric. They use 90% a.i. captan which arrives in 50 lb. bags. The bags are manually dumped into a mixer by a worker (2 bags per batch). The worker wears rubber gloves, a respirator, and a company supplied uniform. The mixing area has an exhaust fan to remove particles/dust and workers are required to wear dust masks if they frequent the mixing area. The adhesive mix is then added to the laminator with an automatic pump.

Exposure (Application)

It appears from the description little exposure is incurred. Ordinarily, it would be improper to assume little exposure for this application, but based on the controls and protective clothing and since this is the only plant currently using captan (11,000 lbs/year), the exposure for this particular use seems negligible.

Exposure (Use)

There is extensive use of captan-containing bedding (mattresses and pillows); the use is primarily institutional e.g. hospitals, nursing homes, etc. The treated material is often in skin contact with persons and in a possibly wet environment. Untreated fabric rubbed across treated fabric imparts the former with antimicrobial activity implying transfer of captan from the surface of the treated material. For the exposure estimation, the Agency assumed that in some situations (e.g. psychiatric hospitals) there may be no covering over the mattresses and pillows. The dermal exposure, as calculated below, is 6 mg/day (0.003 mg/kg/day).

Exposure Estimation

In a previous exposure situation analagous to captan, vinyl material was treated with OBPA (10, 10-Oxybisphenoxarsine). This compound has the same purpose and is used in vinyl materials. Below is a comparision of their properties:

Property	Captan	OBPA
% use concentration w/w	0.3	0.03
Vapor pressure mm Hg	$1X10^{-5}$	$1X10^{-6}$
Water solubility ppm	<0.5	10
Molecular Weight	301	502

Inhalation Exposure

The Agency has no monitoring data to estimate the concentration of captan in the air from use in mattresses and pillows, but

assumes the exposure is negligible, because the concentration is low (0.3%), the vapor pressure is low, and the captan is contained in a vinyl matrix.

Dermal Exposure

In the OBPA exposure estimate, marine upholstery leached at a rate of 12.1 $mg/m^2/24$ hour period. Subsequent leaching of this material produced less than 50% of the amount. Assuming OBPA and captan have similar leaching propensity, but taking into account concentration and water solubility, a worst case estimate of possible dermal exposure can be made.

$$12.1\ mg/m^2/day \times \frac{0.3}{0.03}\ (\text{conc. factor}) \times \frac{0.5}{10}\ (\text{sol. factor}) \times$$

$1\ m^2$ (half body area) = 6 mg/day (0.003 mg/kg/day)

The Agency assumes that this would be significantly reduced if the mattresses and pillows were covered as is the normal practice in hospitals and nursing homes.

2) Adhesives

The use of captan in adhesives is primarily in the production of wallpaper flour adhesives. Captan is used to prevent fungal growth in the dry paste adhesive, later when water is added, and as protection against fungi when paper is exposed to moisture or humid conditions. Unprotected adhesive would, if moisture is present, be attacked by fungi and result in loss of integrity of the bonding.

Use as an Additive

The only significant adhesive use of captan is in the production of wallpaper adhesive paste. This use consumes 5000 lb 90% a.i. product per year. With the advent of resin based adhesives which may not require water, and the use of other preservatives, captan use has decreased to such an extent that its use is limited to one plant in Iowa which still utilizes captan in making one type of wallpaper adhesive.

The captan product (Vancide 89, 90% a.i.) is added to the flour paste at the rate of 0.6% w/w. The formulation arrives in 50 pound drums and is weighed out 48 pounds at a time. This amount is used per 24 hour period. This operation requires about two minutes.

Gloves and respirator are worn during the weighing operation. The total amount is then added to an automatic feed device (about 30 seconds; no protective clothing) and added to the starch/water paste mixture and dried (300°F) on rollers. During the 30 second period where no protective clothing is worn, exposure to the hands is possible. The Agency assumes the

applicator will be exposed to 200 mg/day, covering the surfaces of both hands (Day, 1984b). The dried product is subsequently scraped off, ground up, and bagged for shipment. A ventilation hood is located over the roll dryers to carry away vapors.

Exposure (Application)

Although the Mitre Report claims exposure is minimal, there are several opportunities for exposure to workers.

Operation	Exposure
Weighing	Probably negligible due to protective clothing.
Addition	Inhalation/dermal exposure
Drying	Inhalation
Packaging	Inhalation
General Work Area	Inhalation

Exposure (Use)

The packaged wallpaper adhesive contains about 0.6% captan and is widely distributed for use. Workers who pour/measure out the adhesive, and use it for glueing wallpaper could receive some exposure during mixing and application.

3) Paints

Captan is registered for use as a biocide in paint formulations. They fall into three areas: in-container preservative, mildewcide for dry paint films, and antifoulants for marine applications. Annual consumption of captan in the paint industry is estimated at 50,000 lbs. Less than 1% of the paint manufacturers (about 10) use captan. There are many alternative biocides available and in use.

Use as an Additive

The paints containing captan are usually formulated for special situations, such as breweries and sugar refineries, where high humidity promotes the growth of fungi. Captan is added to the level of 1% w/w.

Only one plant was identified in the survey as being an active user of captan. The plant has manufactured a paint designed for use in sugar refineries for 15 years. Vancide 89 (90% a.i. captan) is received in 55 pound drums. It is added to the paint formulation at the mixing stage. About 5-7 pounds of Vanicide is weighed out and sifted into the formulation from a

paper bag. Application time is about one minute. Gloves and respirator are worn for this application. The paint is then canned and packaged for shipment. Only about 10 batches of this paint are produced yearly.

Exposure (Application)

The Mitre report claims an annual use of 50,000 lbs; yet the only paint plant found used only 100 lbs. per year. This is a large discrepancy. It could be that the larger total use figure is outdated and other products are now being used instead. Captan has the undesirable trait of causing a color shift in paint over a period of time.

For worker exposure, potential inhalation and dermal exposure are likely to be mitigated by wearing gloves and a respirator during the weighing and addition operation. This may not be true at other unidentified plants that manufacture captan-containing paint. No mention was made about cleanup operations of the formulation areas which could result in exposure if protective clothing is not used.

Exposure (User)

The paint as received for use contains 1% captan. A painter using either a brush or sprayer could receive dermal exposure from the paint (6 grams of paint/day 10 days/year). This may be particularly significant because they are generally oil base paints which may enhance dermal absorption.

4) Cosmetics

Captan is registered for use with the Food and Drug Administration (FDA) as an antimicrobial agent in cosmetic formulations which include perfume, cosmetics, shampoo and shaving products. The cosmetics containing captan are regulated by the FDA.

Use as an Additive

Captan is used to prevent microbial growth in the cosmetic formulations; also they inhibit growth of fungi/bacteria on the skin. Some dandruff shampoos incorporate captan as an active ingredient. Protection of the cosmetic is particularly important in the case of oil-in-water emulsions.

The only captan product registered with the EPA for formaltion into a powdered hand soap is Vancide 89 which contains 87% captan. To make the sanitizing deodorant powdered hand soap, 1% Vancide 89 is added by weight of the anhydrous soap. (It is also used in wallpaper paste and rubber coated articles.) Another captan product, PETRX, is registered with EPA for use as a dog or cat shampoo; the insecticide in the product kills fleas and lice while captan controls fungal growth on the animal's skin.

There are 36 cosmetic products registered with EPA and FDA that contain captan. Total usage of captan in these products was estimated at 50,000 lbs. in 1980. Captan is added at the rate of 0.1-0.2% w/w for simple aqueous solutions and 0.2-0.5% w/w for creams and emulsions. The use of captan as a preservative is still important, but declining. Many substitutes exist for captan.

Exposure (Application)

Captan is received in 20-25 kg drums and is weighed out by one worker who wears a dust mask, gloves and disposable apron. The operation requires about two minutes and is performed about 36 times per year. After mixing there is no further direct worker exposure.

Exposure (User)

The cosmetic products listed in the Mitre report cover a wide range of products: shampoo for humans and animals, toothpaste, lotions, creams, etc. Application results in both dermal and oral exposure. Many of these products can be characterized as being absorbed completely by the skin; therefore the captan present would also be carried into the skin at a rate approaching 100% (0.833 mg/kg/day). These products are regulated by the FDA, except for Vancide 89 and animal shampoos or dusts which are regulated by EPA.

5) Other Uses

Captan is also incorporated in aerosol sprays, pet powders and packing boxes. Exposure from use of these products was estimated by the Agency as follows (Reinert, 1985):

Surface Sprays

Captan is added to spray formulations used for surface treatment of awnings, clothing, drapes, rugs, etc. at 0.04% and to spray formulations used on pets at 0.25%. For a model to estimate exposure from aerosol pet spray the study by Staiff (1975) is the most appropriate surrogate. In this study on aerosol can use of paraquat (0.44%) in a yard/garden situation, mean dermal exposure (15 samples-range 0.01 - 0.57 mg/hr) was found to be 0.3 mg/hr. Inhalation exposure was found to be negligible. The Agency assumes the surface sprays will be used for 5 minutes once a week throughout the year.

Pet Powders

Captan is incorporated in some pet powders at the level of 0.5% a.i. The Agency assumes it will be used once a week throughout the year and that a person applying pet powder will be exposed to 200 mg per use (Day, 1985).

Packing Boxes

Captan is used as a supplement for wood preservative treatment with inorganic arsenicals. This process involves pressure treatment and captan would be incorporated into the wood and very little would be at the surface. The Agency assumes that that there would not be significant dermal or inhalation exposure from captan in wood used to make packing crates. Thus exposure from this use of captan is estimated to be negligible.

Exposure to humans from use of these end products is summarized as follows:

Dermal Exposure Estimation[1/]

Use	Exposure	Exposure (mg) Daily	Exposure (mg) Yearly	Exposure (mg/kg) Daily	Exposure (mg/kg) Yearly
Aerosol sprays[2/]	0.3 mg/hr	0.025	1.3	0.00036	0.019
Pet powders[3/]	200 mg x (0.005)	1.0	52	0.014	0.74
Packing boxes	Negligible	-	-	-	-

1/ The Agency assumes that inhalation exposure is negligible for these three exposure situations.

2/ The Agency estimates that use is 52 times per year and that 0.3 mg/hr is the mean dermal exposure.

3/ The concentration of captan in pet powders is 0.5% a.i.

6) Summary of Assessment of Exposure from the Various Non-agricultural Uses of Captan

For application of captan it is assumed that protective clothing will eliminate significant exposure. Estimates of exposure for manufacturing and product use are summarized in Tables 17 and 18. The adhesive use, in particular is difficult to quantify because of the heating of captan and the dust formation after drying. Others in the manufacturing plant may be exposed, but no estimate can be made.

Table 17 - Non-Agricultural Application Exposure Estimates

Use	Conc. AI%	Weigh/Applicat. Exposure Period Min. Day	Min. Year	Protect. Clothing	Total Dermal mg/day	Inhalation mg/day	mg Yearly
Plastics	90	1	250	yes	0	0	0
Adhesives	90	2.5	180	yes*	200	10	7560
Paints	90	1	10	yes	0	0	0
Cosmetics	90	2	36	yes	0	0	0

*Protective clothing and respirators worn during weighing of captan, but not during addition period of 0.5 min. All exposure based on the 0.5 min. period. (Mitre Corporation, 1981 and Day, 1984c)

Table 18 - Exposure from Non-Agricultural Product Use (1)

Use	Conc. w/w	Exposure Public	Professionals	Est. quantity of product (gm)	Dermal mg/day	Exposure mg/year
Plastics	0.5-3	neg.	neg.	neg.	neg.	neg.
Adhesives	0.6	yes	yes	6 (2)	36	70, 3600 (2)
Paints (5)	1	neg.	yes	6 (3)	60	600
Cosmetics						
-animal shampoos(5)	0.1-0.5	yes	NA	10 (4)	50	5000
-Powdered soap(6)	0.87	yes	NA	10 (4)	87	9048

(1) Inhalation exposure is negligible due to low vapor pressure.
(2) Assumes contact with 6 gms of wet adhesive for 2 days/year for the public and 100 days/year for the professional user.
(3) Assumes painter will contact 6 gms of paint/day 10 days/yr.
(4) Assumes use of 10 gms lotion/shampoo products twice a week.
(5) The human dermal absorption of these products is assumed to be 100%.
(6) The dermal absorption of these products in water is assumed to be 1.3% (Zendzian, 1982).

(Mitre Corporation, 1981 and Day, 1984c)

4. Risk Characterization

a. Dietary Risk (Food Residues)

The captan dietary risk numbers were derived making the following assumptions (Saito, 1984):

- Residues would be present on crops at tolerance levels, or at market-basket levels.
- EPA food factors (percent of commodity in diet) were used.
- A person eats 1.5 kg of food per day.
- A person weighs 60 kg.
- The Q_1^* for captan was 2.3×10^{-3} $(mg/kg/day)^{-1}$

A sample calculation for apples is provided:

mg of pesticide = tolerance x food factor x 1.5 kg diet

$$\text{mg of pesticide} = \frac{25 \text{ mg}}{\text{kg}} \times 0.0253 \times 1.5 \text{ kg} = 0.949 \text{ mg}$$

$$\frac{\text{mg of pesticides}}{\text{kg of body weight}} = \frac{0.949 \text{ mg}}{60 \text{ kg}} = 0.016 \frac{\text{mg}}{\text{kg}}$$

Risk = Q_1^* x exposure

Risk = 2.3×10^{-3} $(mg/kg/day)^{-1}$ x 0.016 mg/kg/day

Risk = 10^{-4} (B2) to 10^{-5} (B2)

Table 19 presents the dietary risks to the U.S. population based, for comparison purposes, on published tolerances and Market Basket Surveys. The estimates represent the upper limit of excess cancer risk which is not likely to be exceeded.

Accurate data are not yet available on daily intake of captan. The best available data are 7.013 mg/1.5 kg diet/day for a TMRC (Theoretical Maximum Residue Concentration) value and .011 mg/1.5 kg diet/day for intake based on residues from Market Basket Surveys (Jensen, 1982).

These dietary estimates of intake divided by 60 kg approximate the daily intake of captan as .1169 mg/kg (body weight)/day and .00018 mg/kg/day based respectively on tolerances and market basket residues. When multiplied by Q_1^*, the upper 95% bound on cancer risk are:

10^{-3} (B2) to 10^{-4} (B2) based on tolerances
10^{-6} (B2) to 10^{-7} (B2) based on market basket surveys

(Lacayo, 1984)

Table 19 - Estimate of Upper Bound Risk (95% Confidence Level) for Captan Associated with Diet Based on Published Tolerances or Market Basket Surveys[1/]

Crop	For Published Tolerances	For Market Basket[2/]
Potatoes	10^{-4}	
Lettuce	10^{-4} to 10^{-5}	10^{-7} to 10^{-8}
Peaches	10^{-4} to 10^{-5}	10^{-7}
Tomatoes	10^{-4} to 10^{-5}	10^{-7}
Apples	10^{-4} to 10^{-5}	10^{-7}
Beans	10^{-5}	
Oranges	10^{-5}	
Grapes, including raisins	10^{-5}	
Grapefruit	10^{-5}	
Cucumbers, inc pickles	10^{-5}	
Onion (dry bulb)	10^{-5}	
Celery	10^{-5}	
Plums, including prunes	10^{-5}	10^{-9}
Cantaloupe	10^{-5} to 10^{-6}	
Cherries	10^{-5} to 10^{-6}	10^{-8}
Pineapple	10^{-5} to 10^{-6}	
Pears	10^{-5} to 10^{-6}	10^{-8} to 10^{-9}
Apricots	10^{-6}	10^{-7} to 10^{-8}
Onions, green	10^{-6}	
Spinach	10^{-6}	
Strawberries	10^{-6}	10^{-7}
Peppers	10^{-6}	
Lemons	10^{-6}	
Limes	10^{-6}	
Beet greens	10^{-6}	
Pumpkin, including squash	10^{-6}	
Corn, sweet	10^{-6}	
Soybeans (oil)	10^{-6}	
Leeks	10^{-6}	
Mangoes	10^{-6}	
Nectarines	10^{-6}	10^{-9}
Shallots	10^{-6}	
Cabbage, sauerkraut	10^{-6}	
Peas	10^{-6}	
Rhubarb	10^{-6} to 10^{-7}	
Carrots	10^{-6} to 10^{-7}	
Avocados	10^{-6} to 10^{-7}	
Blackberries	10^{-6} to 10^{-7}	10^{-9}
Blueberries	10^{-6} to 10^{-7}	10^{-8}
Crabapples	10-6 to 10-7	
Cranberries	10-6 to 10-7	

Table 19 (continued)

Crop	For Published Tolerances	For Market Basket[2/]
Dewberries	10^{-6} to 10^{-7}	
Eggplant	10^{-6} to 10^{-7}	
Garlic	10^{-6} to 10^{-7}	
Honeydew melons	10^{-6} to 10^{-7}	
Muskmelons	10^{-6} to 10^{-7}	
Pimentos	10^{-6} to 10^{-7}	
Quinces	10^{-6} to 10^{-7}	
Raspberries	10^{-6} to 10^{-7}	10^{-8}
Summer Squash	10^{-6} to 10^{-7}	
Tangerines	10^{-6} to 10^{-7}	
Winter Squash	10^{-6} to 10^{-7}	
Beets	10^{-7}	
Cattle	10^{-7}	
Cottonseed (oil)	10^{-7}	
Broccoli	10^{-7}	
Hogs	10^{-7}	
Collards	10^{-7}	
Cauliflower	10^{-7} to 10^{-8}	
Mustard Greens	10^{-7} to 10^{-8}	
Brussels Sprouts	10^{-8}	
Kale	10^{-8}	
Rutabagas	10^{-8}	
Almonds	10^{-8}	10^{-10} to 10^{-11}
Taro	10^{-8} to 10^{-9}	

1/ Captan is classified as a Probable Human Carcinogen (Group B2) in accordance with the Agency's Proposed Guidelines (U.S. EPA, 1984, 49 FR 46294).

2/ Based on Stauffer Chemical Company Market Basket Surveys (1979), Chevron Chemical Company Market Basket Survey (1978), Canadian residue data (Stalker, 1981), FDA monitoring programs for 1978-1981 (Gunderson, 1982).

The above values summarize the risks for all the individual crops shown, taking into account the percentage of the particular food in a person's diet each day. The values do not take into account the percent of the crop treated with captan. The percent crop treated was not used due to lack of marketing information which shows that the treated crop would be distributed and diluted nationally. However, if such information were provided, the Agency may be able to use the percent crop treated where justified.

Because tolerances indicate the residues which could legally be present on crops, the Agency will base its proposed regulatory action (agricultural uses) on the total dietary risk of 10^{-3} (B2) to 10^{-4} (B2) based on established tolerances. The residues actually on the crops are probably not that high, but the Agency has no other data on which to base a regulatory decision for risk from dietary exposure to all food crops in a person's diet.

Captan was registered for use on seeds without submission of data to establish tolerances for the plants which grow from the seeds and which, therefore, may contain residues of captan and/or its metabolites. Although the Agency does not have data for residues in plants which might result from seed treatment, it is assuming, for the present, that the resulting residues would be at or below the limit of detection, and that dietary risks to humans would be insignificant. The Agency will be requesting such residue data.

For detreated (washed) corn seed fed to animals, the Agency expects no residues to result in cattle or hogs as long as treated corn seeds are detreated to reduce captan to the 100 ppm tolerance and as long as a 14-day pre-slaughter interval is observed. Thus, no residues are expected to result from the use of detreated corn seed to feed cattle and hogs. The tolerance and pre-slaughter interval were based on feeding studies submitted by Chevron.

b. Applicator and Mixer/Loader Risk

To estimate dermal absorption and risk to applicators and mixer/loaders, the following steps and/or assumptions were used (Day, 1984a and Lacayo, 1984).

1) Calculate the agent arrival rate, r, in milligrams per hour. For example, if a worker is exposed to 100 mg/day of Captan, then in a typical 8-hour work day, the arrival rate is 100/8 = 12.5 mg/hour.

2) Calculate the mg/day absorbed by the worker using the formula:

$$\text{Total Agent Absorbed} = A(h,a,r)$$

$$= r\left[(h+1) - (1/a)\left(1-(1-a)^{h+1}\right)\right]$$

where r = arrival rate of agent in milligrams per hour.

h = total number of hours exposed (6 hrs).

a = absorption rate per hour of the amount of agent present (1.3% per hour from Zendzian, 1982 and Lacayo, 1984).

then the worker dose in mg/kg/day is $A(h,a,r)/70$.

The dermal absorption of 1.3% per hour is based on a study in rats submitted by Stauffer (1982b) and evaluated by the Agency (Zendzian, 1982). The Agency assumes a 100% inhalation absorption rate (Lacayo, 1984).

3) Calculate the Lifetime Average Daily Dose (LADD) using the formula

LADD = (Dose acquired in 1 working day in mg/kg/day)

x (No. of days exposed per year/365)

x (35 years of working)/(70 years lifetime).

4) Calculate the LADD risk using the formula

LADD Risk = LADD x Q_1*; where Q_1* = 2.3 x 10^{-3} $(mg/kg/day)^{-1}$

In calculating exposure, it is assumed that farm workers may work from a low of 1 hour to a high of 12 hours per day. They may wash up immediately after spraying, or not until the end of the work day. Steps 1 thru 4 assume an 8-hour work day (with the exception of Almonds and Home Gardens) and a steady accumulation of the chemical on the skin throughout the day. It is also assumed that workers wash immediately at the end of the 8-hour work day.

The mixer/loader and applicator risks for crops are given in Tables 20 and 21. Risks for workers with protective clothing can be obtained from these tables by multiplying them by 0.2. It can be seen from these tables that potential oncogenic risk to applicators from dermal and inhalation exposure to captan ranges from a maximum of 10^{-5} (B2) (e.g., apples, pre-harvest) to 10^{-7} (B2) (home gardens and pilots for almond applications). The oncogenic risk to mixer/loaders ranges from 10^{-5} (B2) to 10^{-7} (B2). As can be seen in Tables 10 and 11 in Section II.C.3.a.1. of this document, dermal exposure far exceeds respiratory exposure for applicators and for mixer/loaders; the estimates, therefore, in Tables 20 and 21 represent potential risk largely due to dermal exposure. However, in some cases, as in cranberries, the inhalation exposure is not insignificant and does add appreciably to total risk.

These estimates reflect the upper limit of excess cancer risk which is not likely to be exceeded.

Table 20 - Mixer/Loader Risk Estimates
(No Protective Clothing)

Fruit Crops	Maximum Number of Days of Exposure per Year	Maximum Lifetime Average Daily Dose Risk[1/]
Almonds	2	10^{-5} to 10^{-6}
Apples (preharvest)	10	10^{-6}
Apples (postharvest)	30	10^{-6}
Apricots	4	10^{-6}
Avocado	4	10^{-6}
Blackberry	5	10^{-6}
Blueberry	10	10^{-5} to 10^{-6}
Cherries	10	10^{-5} to 10^{-6}
Citrus	2	10^{-6} to 10^{-7}
Cranberry	3	10^{-6}
Grapes	6	10^{-6}
Mangos	12	10^{-5} to 10^{-6}
Nectarine	5	10^{-6}
Peaches	5	10^{-6}
Pears	4	10^{-6}
Plum	7	10^{-6}
Pineapple	8	10^{-6}
Vegetable Crop		
Beans	8	10^{-6}
Beets	7	10^{-6}
Carrots	8	10^{-6}
Celery	13	10^{-5} to 10^{-6}
Cucurbits	13	10^{-5} to 10^{-6}
Eggplant	14	10^{-5} to 10^{-6}
Lettuce	8	10^{-6}
Peppers	20	10^{-5} to 10^{-6}
Potatoes (foliar)	17	10^{-5} to 10^{-6}
Potatoes (seed treat.)	5	10^{-6} to 10^{-7}
Rhubarb	10	10^{-5} to 10^{-6}
Soybeans (seed treat.)	2	10^{-6} to 10^{-7}
Spinach	4	10^{-6}
Sweetcorn	10	10^{-5} to 10^{-6}
Tomatoes	13	10^{-5} to 10^{-6}
Ornamentals		
Azaleas	4	10^{-6}
Begonias	12	10^{-5} to 10^{-6}
Carnations	20	10^{-5} to 10^{-6}
Mums	20	10^{-5} to 10^{-6}
Diconda (CA)	3	10^{-6}
Turf	20	10^{-5} to 10^{-6}
Roses	20	10^{-5} to 10^{-6}
Flowers	15	10^{-5} to 10^{-6}

1/ Captan is classified as a Probable Human Carcinogen (Group B2) in accordance with the Agency's Proposed Guidelines (U.S. EPA, 1984, 49 FR 46294).

Table 21 - Applicator Exposure and Risk Estimates
(No Protective Clothing)

Fruit Crops	Arrival Rate r (mg/hr)	Dermal[1/] (mg/day)	Inh (mg/day)	Dose[2/] (mg/kg/day)	Maximum Days	Maximum[3/4/5/] Lifetime Average Daily Dose Risk
Almonds (pilot)	2.27	0.4	neg.	.006	2	10^{-7}
Apples (pre-harvest)	30.0	8.014	0.06	.115	10	10^{-5} to 10^{-6}
Apricots	35.0	9.35	0.06	.134	4	10^{-6}
Avocado	35.0	9.35	0.06	.134	4	10^{-6}
Blackberry	24.0	6.4	0.06	.092	5	10^{-6}
Blueberry	24.0	6.4	0.06	.092	10	10^{-6}
Cherries	35.0	9.35	0.06	.134	10	10^{-5} to 10^{-6}
Citrus	35.0	9.35	0.06	.134	2	10^{-6} to 10^{-7}
Cranberry	24.0	6.4	0.06	.092	3	10^{-6}
Grapes	24.0	6.4	0.06	.092	6	10^{-6}
Mangos	40.0	18.2	0.06	.154	12	10^{-5} to 10^{-6}
Nectarine	40.0	10.7	0.06	.154	5	10^{-6}
Peaches	40.0	10.7	0.06	.154	5	10^{-6}
Pears	28.0	7.5	0.06	.108	4	10^{-6} to 10^{-7}
Plum	30.0	8.0	0.06	.115	7	10^{-6}
Pineapple	24.0	6.4	0.06	.092	8	10^{-5} to 10^{-6}
Vegetable Crop						
Beans	24.0	6.4	0.06	.092	8	10^{-6}
Beets	24.0	6.4	0.06	.092	7	10^{-6}
Carrots	24.0	6.4	0.06	.092	8	10^{-6}
Celery	24.0	6.4	0.06	.092	13	10^{-5} to 10^{-6}
Cucurbits	24.0	6.4	0.06	.092	13	10^{-5} to 10^{-6}
Eggplant	24.0	6.4	0.06	.092	14	10^{-5} to 10^{-6}
Lettuce	24.0	6.4	0.06	.092	8	10^{-6}
Peppers	24.0	6.4	0.06	.092	20	10^{-5} to 10^{-6}
Potatoes — (foliar)	24.0	6.4	0.06	.092	17	10^{-5} to 10^{-6}
Potatoes — (seed treatment)	0.35	0.09	0.20	.004	5	10^{-7}
Rhubarb	1.7	0.77	0.0017	.035	10	10^{-6} to 10^{-7}
Spinach	24.0	6.4	0.06	.092	4	10^{-6}
Strawberries	24.0	6.4	0.06	.092	10	10^{-6}
Sweetcorn	24.0	6.4	0.06	.092	10	10^{-5} to 10^{-6}
Tomatoes	24.0	6.4	0.06	.092	13	10^{-5} to 10^{-6}
Home and Garden	1.7	0.45	0.0017	.067	4	10^{-7}
Ornamentals						
Azaleas	24.0	6.4	0.06	.092	4	10^{-6}
Begonias	24.0	6.4	0.06	.092	12	10^{-5} to 10^{-6}
Carnations	24.0	6.4	0.06	.092	20	10^{-5} to 10^{-6}
Mums	24.0	6.4	0.06	.092	20	10^{-5} to 10^{-6}

Table 21 - (continued)

Fruit Crops	Arrival Rate r (mg/hr)	Dermal[1/] (mg/day)	Inh (mg/day)	Dose[2/] (mg/kg/day)	Maximum Days	Maximum[3/4/5/] Lifetime Average Daily Dose Risk
Diconda (CA)	24.0	6.4	0.06	.092	3	10^{-6}
Turf	24.0	6.4	0.06	.092	20	10^{-5} to 10^{-6}
Roses	24.0	6.4	0.06	.092	20	10^{-5} to 10^{-6}
Flowers	24.0	6.4	0.06	.092	15	10^{-5} to 10^{-6}

1/ Based on $A(h,a,r) = r[(h+1)-(1/a)(1-(1-a)^{h+1})]$ with h = 6 hours, r = arrival rate, a = 1.3% dermal absroption rate, and a 100% inhalation absorption rate.

2/ Dose = (Dermal + Inh)/70 (mg/kg/day)

3/ Maximum LADD Risk = Q_1^* Dose x (# exposed day/365) x (35/70)

4/ Captan is classified as a Probable Human Carcinogen (Group B2) in accordance the Agency's proposed guidelines (U.S. EPA, 1984, 49 FR 46294).

5/ Lacayo, 1985. Risks for workers with protective clothing can be obtained by multiplying the risks by 0.2.

c. Risk to Fieldworkers

The risk estimates for fieldworkers were calculated using exposure data on strawberries (Adams, 1984) described previously in this position documented in Section II.C.1.b. The following formulas were used (Lacayo, 1984):

1) Estimate of Daily Dermal Exposure

Total Agent Absorbed = A (h,a,r)

$= r\,[(h + 1) - (1/a)\,(1-(1-a)^{h+1})]$

where r = arrival rate of agent in grams per hour.

h = total number of hours exposed.

a = absorption rate per hour of the amount of agent present (1.3% per hour based on Zendzian, 1982 and Lacayo, 1984).

The worker dose in mg/kg/day is A(h,a,r)/70.

2) Estimate of Life Time Average Daily Dose (LADD)

LADD = (Dose acquired in 1 working day in mg/kg/day)

x (No. of days exposed per year/365)

x (35 years of working)/(70 years lifetime).

3) Estimate of LADD Risk

LADD Risk = LADD x Q_1^* = LADD x $(2.3 \times 10^{-3})(mg/kg/day)^{-1}$

Table 22 presents the exposure and LADD (Lifetime Average Daily Dose) for the seven field exposure studies using residues after application of captan on strawberries. The risk estimates presented reflect the upper limit of excess cancer risk which is not likely to be exceeded (Lacayo, 1984b).

The order of magnitude of risk is unchanged by:

1. Adding the worker dietary risk to the harvesting exposure risk.

2. Having workers both pick and weed strawberries, as in study #3.

Table 22 - Fieldworker Exposure and Risk Estimates for Seven Strawberry Exposure Studies (Adams, 1984 and Lacayo, 1984b)

Study #	Arrival Rate (mg/hr)	Exposure hrs/day	Exposure day/yr	Absorp. per day mg/kg/day	Lifetime Average Daily Dose	Risk[1/]
1	6.5	8	80	.04276	.00528	10^{-5}
2	4.7	8	30	.030488	.00143	10^{-6}
3 Picking	17.41	8	80	.1129	.01414	10^{-5}
Weeding	94.13	8	10	.61060	.009559	10^{-5}
4	16.37	8	80	.106189	.01329	10^{-5}
5	5.88	8	80	.038142	.004779	10^{-5}
6	39.01	8	80	.25305	.031693	10^{-5} to 10^{-4}
7	7.15	8	80	.04638	.0058	10^{-5}

1/ Captan is classified as a Probable Human Carcinogen (Group B2) in accordance with the Agency's Proposed Guidelines (U.S. EPA, 1984, 49 FR 46294).

d. Risk to Workers in Cut Flower Production

The risk estimates to workers mixing, loading and spraying formulations containing captan to flowers and to workers cutting and packaging the flowers were calculated using the exposure data described previously in this document in Section II.C.4.d. The Agency assumes that workers will be exposed over a working lifetime of 35 years. The exposure and risk estimates using $Q_1^* = 2.3 \times 10^{-3}$ $(mg/kg/day)^{-1}$ (Saito, 1985) are presented in Table 23.

Table 23 - Exposure and Risk Estimates for Workers in Cut Flower Production

Operation	Exposure (mg/kg/day) Dermal	Exposure (mg/kg/day) Inhalation	Risk Dermal	Risk Inhalation
Mix/load/spray	0.19	0.002	10^{-7}(B2)	10^{-7}(B2)
Cutting/packaging	0.09	neg.	10^{-6} to 10^{-7}(B2)	neg.

e. Non-Agricultural Uses

Captan is used in plastics, adhesives, paints, cosmetics, and shampoos as an antifungal agent. The potential oncogenic risks associated with these exposures have been calculated by the Agency to range from negligible (e.g., plastics) to 10^{-5}(B2) (e.g., oil-based paints and animal shampoos (Lacayo, 1985).

Regarding cosmetics and shampoos for humans, EPA will transmit all toxicity information to FDA for evaluation and risk assessment purposes, since FDA regulates these products. Because dog and cat shampoos are regulated by EPA, a risk assessment has been calculated for humans who wash their dogs and cats.

As can be seen from Table 24, the potential oncogenic risk to applicators for plastics, paints, and cosmetics is negligible; the risk associated with application of captan to adhesives is 10^{-5} (B2). Table 25 shows that potential oncogenic risks to users of end products containing captan range from 10^{-4} (B2) (animal shampoos) to 10^{-9} (B2) (aerosol sprays). For dog or cat shampoos, the risk to humans is 10^{-4} to 10^{-5} (B2) assuming 10g on the skin at a 0.25% concentration (25mg/day), a person shampooing a dog 4 times a year for 60 years out of a 70 year lifetime, at 100% absorption. The estimated risks reflect the upper limit of excess cancer risk which is not likely to be exceeded.

Table 24 - Risks during Application for Non-Agricultural Uses

Use	Exposure (mg/kg/day)	Risk $Q_1^* = 2.3 \times 10^{-3}$ (mg/kg/day)$^{-1}$
Plastics [1]	negligible	negligible
Adhesives [2]	0.162 (i+d)	10^{-5} (B2)
Paints [1]	negligible	negligible
Cosmetics [1]	negligible	negligible

[1] The Mitre Report (1981) states that gloves, respirator (dust masks for cosmetics incorporation) and protective clothing are normally worn during application/ mixing; thus the exposure and risks are negligible.

[2] Assumes 70 kg person, 2.5 minutes application/hour, 72 days/ year for 40 years of a 70 year lifetime.
For inhalation (i) exposure estimate, assume 100% absorption, 10 mg/day.
For dermal (d) exposure estimate, assume 1.3% absorption of amount present per hour and 200 mg/day exposure.

Table 25 - Risk from Product Use (Non-Agricultural)[1/]

Use	Exposure(mg/kg/day)	Risk $Q_1^* = 2.3 \times 10^{-3}$ (mg/kg/day)$^{-1}$
Plastics	negligible	negligible
Adhesives		
Home Use[2/]	0.0624	10^{-6} to 10^{-7}
Professional[3/]	0.0624	10^{-5}
Paints		
Oil-based[4/]	0.857	10^{-5}
Water-based[5/]	0.089	10^{-6}
Shampoos for animals[6/]	0.416	10^{-4} to 10^{-5}
Mattresses[7/]	0.013 (dermal)	10^{-5} to 10^{-6}
Aerosol sprays[8/]	0.00036	10^{-9}
Pet powders[9/]	0.014	10^{-8}
Powdered hand soap[10/]	0.016	10^{-5} to 10^{-6}

1/ Captan is classified as a Probable Human Carcinogen (Group B2) in accordance with the Agency's Proposed Guidelines (U.S. EPA, 1984, 49 FR 46294).

(Footnotes to Table 25 continued)

2/ For home use of adhesives, assume a 60 kg person, 36 mg/day dermal exposure, 8 hours/day, 2 days/year for 40 years of a 70 year lifetime, 1.3% dermal absorption per hour.

3/ For professional use of adhesives, assume a 60 kg person, 36 mg/day dermal exposure, 8 hours/day, 100 days/year for 40 years of a 70 year lifetime 1.3% dermal absorption/hour.

4/ For oil-based paints, assume a 60 kg person, 60 mg/day dermal exposure, 8 hours/day, 10 days/year for 40 years of a 70 year lifetime and 100% dermal absorption due to oil base or varnish as a vehicle containing the captan.

5/ For water-based paints, assume a 60 kg person, 60 mg/day dermal exposure, 8 hours/day, 10 days/year for 40 years of a 70 year lifetime and 1.3% dermal absorption per hour.

6/ For shampoos (dog or cat being washed by a person) assume a 60 kg person, 50 mg dermal exposure per day (10 g shampoo x 0.5% W/W = 50 mg), 4 times a year for 60 years of a 70 year lifetime and 100% dermal absorption due to the presence of oil/water emulsion, glycerine, or triethanolamine stearic acid soap.

7/ For mattresses in nursing homes, assume a 60 kg person, 6.0 mg/day dermal exposure at 1.3% dermal absorption per hour, 10 years in a nursing home over a 70 year lifetime. The Agency assumes that coverings will reduce the exposure at least by an order of magnitude.

8/ For aerosol sprays, assume negligible inhalation exposure, 0.3 mg/hr (mean dermal exposure at 100% dermal absorption) for 5 minutes once a week throughout the year for 35 years of a 70 year lifetime.

9/ For human exposure to pet powders, assume negligible inhalation exposure, 200 mg dermal exposure (at 100% dermal absorption) per use once a week throughout the year for 35 years of a person's 70 year lifetime.

10/ For a sanitizing powdered hand soap, assume a 60 kg person, 87 mg/day exposure at 1.3% dermal absorption, twice a week for 35 years out of a person's 70 year lifetime.

f. Uncertainties in the Risk Assessment

The risk assessment approach contains a number of uncertainties.

The quantitative risk estimates contain a great deal of uncertainty because they must necessarily extrapolate from laboratory animals to humans and from the very high exposures

used in the laboratory studies to the generally much lower and less well characterized human exposures. The Agency's approach has been to present plausible upper bounds to the risk as a rough indication of what the potential risks might be.

Dietary exposure estimates are a source of uncertainties, some of which have been discussed in section II.C.4.a.(4 and 5.) Tolerance levels were used to calculate a worst-case risk estimate. Insufficient data are available on residues likely to be present on food as consumed. In order to avoid suspension under FIFRA 3(c)(2)(B) data call-in provisions, the registrant must submit such data in the near future.

Variation in individual food intake patterns is another source of uncertainty in estimating health risks from dietary exposure to captan. The dietary burdens in the dietary exposure tables (Tables 14 and 15) were based upon standard food factors used by the Agency for many years to represent typical diets. Although these standard food factors are appropriate for estimating average population risk, some individuals and subgroups within the population will be at greater (or lesser) risk because their diets contain more (or less) of the food with captan residues.

Similarly, there are variations in the amount of food consumed as a "single serving". The Agency calculated the "single serving" from information available in the USDA report, "Family Food Buying (USDA, 1977).

Uncertainties also exist in the area of applicator exposure and risk, and the primary uncertainty in this area relates to time spent in applying captan, the number of applications made per year, the duration of each application, and the number of years a person would be applying captan are all highly variable.

D. TERATOGENIC RISK ASSESSMENT

The "single serving" dietary exposure assessment, as described in Section II.C.3.a., makes it possible to calculate teratology margin of safety (MOS) for captan dietary exposure (Schneider, 1982).

The results of a study using Syrian Golden Hamsters (Robens, 1970) were suggestive for teratogenic effects with a no-observed-effect-level (NOEL) of 200 mg/kg/day. The allowable daily intake for a 60 kg woman would be 12,000 mg/day (200 mg/kg/day x 60 kg). The lowest MOS is 828 for cherries (Table 26). However, because there were omissions and/or inconsistencies in the tabular data and because statistical analyses were not performed in this study, the Agency will require an additional teratology study in hamsters to better evaluate these effects.

Table 26 - Teratogenic Margins of Safety for Various Crops From Dietary Exposure to Captan

Food Commodity or Grouping	Single Serving[1/] (kg)	Tolerance (ppm)	Daily Intake (mg/day)	(MOS)[2/]
Almonds	Unknown	2.00	-	-
Apples	0.212	25.00	5.30	2264
Apricots	0.114	50.00	5.70	2105
Avocados	0.150	25.00	3.75	3200
Beans, Lima (Fresh)	0.072	25.00	1.80	6667
Bean, Snap (Fresh)	0.055	25.00	1.38	8696
Beet Greens	0.076	100.00	7.60	1570
Beets	0.080	2.00	0.16	75000
Blackberries	0.072	25.00	1.80	6667
Blueberries	0.072	25.00	1.80	6667
Broccoli	0.092	25.00	0.18	66667
Brussels sprouts	0.078	2.00	0.16	75000
Cabbage, Sauerkraut	0.090	2.00	0.18	66667
Cantalopes	0.160	25.00	4.00	3000
Carrots	0.110	2.00	0.22	54546
Cauliflower	0.115	2.00	0.23	52174
Celery	0.120	50.00	3.00	4000
Cherries	0.145	100.00	14.50	828
Collards	0.095	2.00	0.19	63158
Corn, Sweet	0.080	2.00	0.16	75000
Cottonseed	Unknown	2.00	-	-
Crabapples	Unknown	25.00	-	-
Cranberries	0.070	25.00	1.75	6857
Cucumbers, Pickles	0.144	25.00	3.60	3333
Dewberries	0.072	25.00	1.80	6667
Eggplant	0.100	25.00	2.50	4800
Garlic	0.003	25.00	0.08	15000
Grapefruit	0.101	25.00	2.50	4800
Grapes	0.080	50.00	4.00	3000
Raisins	0.145	50.00	7.25	1655
Honeydew melons	0.170	25.00	4.25	2824
Kale	0.055	2.00	0.11	109091
Leeks	Unknown	50.00	-	-
Lemons	0.016	25.00	0.40	30000
Lettuce	0.057	100.00	5.70	2105
Limes	0.016	25.00	0.40	30000
Mangoes	0.082	50.00	4.10	2927
Muskmelons	0.160	25.00	4.00	3000
Mustard greens	0.070	2.00	0.14	85714
Nectarines	0.150	50.00	7.50	1600
Onions, dry bulbs	0.171	25.00	4.28	2804
Onions, green	0.025	50.00	1.25	9600
Oranges, juice	0.245	25.00	6.12	1961
Peaches	0.152	50.00	7.60	1579
Pears	0.180	25.00	4.50	2667
Peas, dried	0.200	2.00	0.40	30000

Table 26 (continued)

Food Commodity or Grouping	Single Serving[1/] (kg)	Tolerance (ppm)	Daily Intake (mg/day)	(MOS)[2/]
Peppers	0.100	25.00	2.50	4800
Pimentos	0.018	25.00	0.45	26667
Pineapple	0.084	25.00	2.10	5714
Plums, prunes	0.070	50.00	3.50	3428
Potatoes	0.169	25.00	4.22	2844
Pumpkin	0.245	25.00	6.12	1961
Quinces	Unknown	25.00	-	-
Raspberries	0.072	25.00	1.80	6667
Rhubarb	0.122	25.00	3.05	3934
Rutabagas	0.120	2.00	0.24	50000
Shallots	0.010	50.00	0.50	24000
Soybeans (Curd)	0.120	2.00	0.24	50000
Spinach	0.055	100.00	5.50	2182
Winter Squash	0.222	25.00	5.55	2162
Strawberries	0.075	25.00	1.88	6383
Summer Squash	0.120	25.00	3.00	4000
Tangerines	0.100	25.00	2.50	4800
Taro	Unknown	0.250	-	-
Tomatoes	0.181	25.00	4.52	2655
Turnips	0.130	2.00	0.26	46154
Turnip Greens	0.072	2.00	0.14	85714
Watermelon	0.160	25.00	4.00	3000

1/ Source: USDA, 1977

2/ Margin of Safety

E. REPRODUCTIVE RISK ASSESSMENT

Section II.B.2. presented laboratory animal studies which showed that captan caused impaired growth of offspring. The NOEL for toxic effects seen in the reproduction studies is 12.5 mg/kg/day and the lowest-effect-level (LEL) is 25 mg/kg/day. To determine whether there is an adequate margin of safety (MOS) between the NOEL for toxic effects and dietary residue levels to which humans might be exposed, the Agency made the following calculations:

- The allowable daily intake (ADI) based on the NOEL of 12.5 mg/kg/day and a safety factor of 100 would be 0.125 mg/kg/day.

- For a 60 kg person, the ADI translates into a maximum permissable intake (MPI) of 7.5 mg/day.

- The theoretical maximum residue contribution (TMRC) assumes that an average person consumes an average (1.5 kg) daily diet with the crops containing tolerance levels of the captan residues. The TMRC is 12.2 mg/day.

- The TMRC exceeds the ADI by 63%. The Agency recognizes that dietary residues may not occur at tolerance levels, no data are available to allow better estimation of the actual dietary residues. When such data are submitted, the Agency will reassess the established tolerances.

III. BENEFITS SUMMARY

A. INTRODUCTION

Captan is a fungicide produced domestically and is also imported from Israel and Taiwan. Total usage of captan in the United States is estimated at 9 to 10 million pounds active ingredient per year. Treatment sites include apples, peaches, almonds, soybean seeds, strawberries, corn, potato seed pieces, cotton, sorghum, peanuts, and numerous other crops (Table 1).

The information used to estimate the benefits of captan was derived from several sources - the U.S. Department of Agriculture, States, and EPA assessment report (Jacobsen, 1982; team leader), the Chevron and Stauffer Chemical Companies (Chevron, 1980, Stauffer, 1980), and analyses produced under cooperative agreements between the EPA and various State Universities (Anderson and Allison, 1983; Drake et al. 1981; Galt et al. 1983; Grube, 1983; Norton et al. 1982; Ofiara et al. 1983; and Wichelns et al. 1982). The general approach of this analysis was to evaluate the economic impacts of a captan cancellation causing users to shift to alternative disease control programs. The alternatives to captan were chosen on the bases of cost, efficacy, and market availability.

Economic impacts on society, as well as for users and consumers, were based on changes in production costs, crop yield reductions, and possible grower shifts to other enterprises. Impacts on users were considered on a per-unit and per-establishment basis as well as at the state, regional, and national levels. Grower level impacts were then utilized for projections at the commodity market levels. The commodity market impacts were then used for estimating the distribution of impacts among consumers, users, and non-users. The sensitivity of these estimates to changes in disease control data and production losses have been examined and indicate these estimates are most representative of the expected impacts.

Cancellation of all current uses of captan are expected to result in first year lost benefits of $20 to $44 million at the farm level, which represents both increased costs of disease control and decreased value of production. In calculating these impacts, it was assumed that only currently registered pest control methods would be available at the time of a captan cancellation. It is expected that for fruits and vegetables the burden would be largely borne by the consumer since large portions of the crops are treated, and market conditions are such that the economic impacts could be transmitted through the marketing system to the retail level. For seed treatment it is expected the burden would be borne by the farmer or seed conditioner since marketing conditions are indicative of excessive supply for produced commodities.

Table 1. Estimated Captan Usage and Benefits of Use

Site	Captan use (pounds a.i.) (1,000)	Acres planted (1,000)	Acres treated (1,000)	Annual impact	
				Total ($1,000)	Per Acre ($)
Fruits and Vegetables					
Apples	2,934	500	169-172	900 to 3,300	5.30 to 19.60
Almonds	897	317	188	1,405	7.47
Bushberries	109-148	71	19-23	3,500 to 4,000	174.00 to 184.00
Apricots	128-160	25	17	-434 to 700	-25.53 to 41.18
Nectarines	108-135	16	11.6	-1 to 654	-0.09 to 56.38
Peaches	1,092	188	121	2,300 to 5,000	19.00 to 41.32
Pineapples	11	44	9	0 to 3,775	0.00 to 413.92
Strawberries	669-870	36	30	5,950	198.73
Others	338-565	NA	120	1,200 to 3,000	10.00 to 26.67
Seed Treatments a/					
Corn	676	81,000	81,000	1,400	0.02
Cotton	275	14,000	11,500	0	0
Sorghum	100	14,500	10,400	1,900	0.10
Soybeans	880	73,620	14,300	-6,200 to 3,400	-0.43 to 0.24
Peanuts	76	1,350	770	146	0.19
Rice	22	3,000	309	35	0.17
Small Grains	97	96,777	2,800	391	0.14
Potatoes	565	1,300	377	-192 to 532	-0.51 to 1.41
Vegetables	235	NA	NA	up to 1,500	NA
Other Sites					
Home Gardens	100	NA	NA	NA	NA
Forest Nurseries	6	17	1	-155 to 1,557	NA
Turf	24	14,000-54,000	5	28	5.60
Ornamentals	45-50	NA	NA	6,000 to 12,600	NA
Total	9,387-9,918			20,000 to 44,000	

a/ The ranges for the grains in this section are somewhat misleading since captan is applied largely by seed suppliers who use captan for a number of different types of seed rather than contend with varying use practices for several types of fungicides.

Impacts on ornamental growers would be borne by the grower since they are already facing substantial foreign competition. Data were not available to estimate whether the burden for forest nurseries and turf would be borne by the user or others.

B. FRUITS AND VEGETABLES

1. Apples

The largest use of captan is for apples, which represents about 30 percent of the total annual usage. Captan is used for control of disease causing fungi on about 170,000 acres of apples or about 34 percent of U.S. commercial apple production.

The loss of captan could result in annual losses of $900,000 to $3,300,000 from the decreased control costs ($600,000 to $900,000) due to lower cost of alternative fungicides and the decreased value of about 40 million pounds of fruit ($1.5 to $4.2 million) annually being diverted from the fresh to the processed market because of increased disease damage with use of alternatives. The following fungicides, within given limitations, are considered to be viable alternatives: metiram, maneb, mancozeb, zineb, thiram, folpet, captafol, dichlone, triforine, and fenarimol. None of the captan alternatives are registered for control of all the apple diseases controlled by captan and some are registered for control of only a few of the diseases for which captan is registered.

A product mixture, Dikar®, containing mancozeb and dinocap is one of the most effective alternatives to captan for use on apples. This mixture is effective against most of the major apple diseases controlled by captan and also controls powdery mildew and rust disease for which captan does not provide adequate control. In Eastern apple production areas where there is a high incidence of heavy apple scab disease, captafol and dichlone are applied in early season application and Dikar® is applied for the remainder of the season.

The primary alternative fungicides expected to be employed are metiram and mancozeb. Use of these alternatives could cause farm level prices to rise by $0.084 per bushel for fresh fruit due to decreased quantities of apples in the fresh market and an ensuing decline of $0.042 per bushel for processing apples due to increased quantities of apples diverted to this market. The new farm level prices could result in increased revenues for growers not using captan. Those growers using captan could suffer losses due to reduced fruit quality associated with Dikar® use. In the aggregate, average changes in producer net revenues per acre would range from a decline of $2.80 to an increase of $2.10. Based on average size apple orchards, on a per farm basis, farmers are

expected to lose on average approximately $530 in net revenues in the Northeast, and $150 in net revenues in the Southeast, but gain $280 in the Central region, and $233 in the West. While these impacts are significant, the farmers facing losses would typically be able to absorb these impacts without major effects on the longer term financial viability of the farms since this represents about a one percent reduction in gross revenues.

Retail prices could increase by $0.172 per bushel for fresh apples due to decreased quantities of apples in fresh markets and decline by $0.172 per bushel for processing due to the increased quantities of apples in this market. Consumer fresh apple expenditures could decline because of the greater influence of the reduction in quantity consumed relative to the expected increase in the retail price. Consumption of processed apples would be expected to increase with the decrease in prices for processed apples. The decrease in consumer expenditures for fresh apples is expected to more than offset the increase in expenditures for processed apples.

2. Almonds

Captan is used on about 188,000 acres of almonds, which represents about 59 percent of U.S. almond acres. The loss of captan use on almonds would result in increased disease control costs of about $1.4 million annually which would be a relatively minor impact on the impacted growers since this represents about one percent of gross income to those currently using captan. Data were not available to estimate the extent these impacts could be shifted to the consumer.

Captan and thiophanate methyl are viable alternative controls for brown rot disease while captan and ziram are the alternative controls for the shothole disease. Therefore, the loss of captan would require use of both materials for control of the diseases currently controlled by captan.

3. Bushberries

Captan is used for disease control on 26 to 32 percent of bushberries (blackberries, boysenberries, blueberries, cranberries, loganberries, and raspberries) acreage. The loss of captan would result in annual losses of $3.5 to $4.0 million (increased disease control costs of $200,000 to $300,000 and production losses of $3.3 to $3.7 million) to those producers using captan. This represents decreased net returns of $174 to $184 per acre which would represent major losses to the impacted growers. These losses represent about 10 percent of gross revenues for those acres treated with captan and although net revenue data were not available, data for other crops indicates this probably would exceed net returns. Data were not available to estimate consumer impacts.

Fruit, leaf and shoot diseases are major problems on bushberries in many of the growing areas. Near harvest time wet weather is particularly conducive to the development of outbreaks of fruit rots which are likely to cause yield losses.

Several fungicides are available which could be used as alternatives to captan. These alternatives include difolatan, 2,6-dichloro-4-nitroaniline (DCNA), and triforine. However, DCNA is the only potential alternative fungicide which can be applied near harvest time.

4. Pineapples

Captan is used as a preplant dip treatment for pineapple rootstock planted on about 20 percent of the 43,000 acres of pineapples grown in Hawaii. It is used to prevent diseases caused by soil borne pathogens.

Alternatives to captan are Aliette®, fenaminosulf, mancozeb, and captafol. Captafol provides equal or superior protection compared to captan, but is not used as a preplant dip because planter exposure results in dermatitis. However, captafol is widely used as a post-plant spray.

Without or with only limited use of captafol, the annual losses associated with a captan cancellation could range up to $3.8 million due to yield losses. If captafol were used as the alternative pineapple production would be maintained at current levels with essentially no change in production costs. This represents a range in losses of from essentially no impact to $400 per acre. If losses of $400 per acre resulted, this could result in some producers shifting out of pineapple production on the affected acres since it is likely that the loss would exceed net returns since this loss is about 20 percent of gross returns. Consumer impacts are not expected since a large portion of the pineapple consumed is already imported and domestic producers have to compete with foreign production.

5. Strawberries

Captan is used on 30,000 acres (about 82 percent of U.S. strawberry acreage) for control of certain fruit and leaf diseases. Alternatives to captan include thiram, benomyl, vinclozolin, and thiophanate methyl. Without captan growers would use some combination of thiram and vinclozolin with an increase in annual disease control costs of about $5.9 million. This represents increased costs of almost $200 per acre which would represent major losses to impacted producers, but may be passed on to the consumer and would only represent a very small change in typical household fresh fruit expenditures.

6. Apricots, Nectarines, and Peaches

Captan is used to control several leaf and fruit diseases on about 61 percent of the bearing acres of apricots, nectarines, and peaches grown commercially in the U.S. Thiophanate methyl, triforine, maneb, benomyl, glyodin, and sulfur are the alternatives most likely to be used to replace captan.

The loss of captan for disease control in apricots would result in an annual economic impact ranging from a decrease in control costs of $434,000 to an increase of $700,000 depending on the alternatives selected, number of applications and application rate. It is unlikely that widespread decreased disease control costs would result.

Nectarine producers could have increased annual disease control costs of up to $650,000 if captan were no longer available.

The loss of captan on peaches could result in annual losses ranging from $2.3 to $5.0 million due to increased disease control costs and lost peach production. Peach producers not requiring the use of captan would experience windfall gains from the increase in peach prices while producers requiring the use of captan would have reduced returns.

It is likely that the apricot and nectarine losses would be borne by the producers while a portion of the peach loss could be shifted to the consumers because of increased peach prices. Although these peach losses could be significant to impacted producers, it is likely they would be passed on to the consumer where the expense would be a very small portion of total household fruit expenditures. The apricot and nectarine losses represent between one and two percent of gross returns and probably are not a threat to the continued viability of the industries.

7. Other Fruits and Vegetables

Captan is registered for use on a number of other fruit crops such as cherries, citrus, grapes, papaya, pears, plums, prunes, taro, as well as several other vegetable crops. The cancellation of captan would result in annual losses ranging from $1.2 to $3.0 million with expected losses approximately $2.0 million (costs of disease control ranging from a decrease of about $400,000 to increased disease control costs of about $1.1 million depending on the alternative fungicide used; and value of production losses of $1.6 to $1.9 million). Data were not available to estimate whether any of these potential losses would be shifted to the consumer. Although data were limited for the loss of captan for these uses, it is unlikely that individual producers or the various industries would be faced with major losses.

Alternatives to captan include: benomyl, thiophenate-methyl, dodine, dichloran, triforine, and chlorothalonil on cherries; captafol, chlorothalonil, and coppers on citrus; ferbam, maneb, mancozeb, dinoseb, sodium arsenite, dichloran, triadimefon, and fenarimol on grapes; ferbam, sulfur, dichlone, coppers, triademefon, chlorothalonil, dichloran, and ziram on plums and prunes with severe efficacy limitations; coppers on avocados; maneb, chlorothalonil, dichloran, and coppers on beans; zineb, ziram, and coppers on beets; captafol, folpet, chlorothalonil, metalaxyl, dichloran, mancozeb, and maneb on cucurbits; chlorothalonil, mancozeb, maneb, and zineb on carrots; analazine, folpet, chlorothalonil, dichloran, mancozeb, maneb, and zineb on celery; mancozeb, maneb, and zineb on eggplant and peppers; folpet, maneb, zineb, dichloran, and vinclozolin and lettuce, captafol, chlorothalonil, metalaxyl, triphenyltin hydroxide, metiram, mancozeb, and maneb on potatoes; folpet, dichloran, captafol, mancozeb, maneb, and zineb on onions; captafol, metiram, chlorothalonil, folpet, maneb, mancozeb, metalaxyl, and zineb on tomatoes; chlorothalonil, maneb, and zineb on spinach; and dichloran on greenhouse rubarb.

C. SEED TREATMENTS

Captan is used as a seed treatment for a variety of crops with the major use being field corn where nearly all of the planted seed is treated with captan. Major portions of the peanut, sorghum, and soybean seed, and seed piece potatoes are also treated with captan. Other seeds treated include barley, oats, rice, rye, and various vegetables. Estimated losses would be less than 50 cents per acre for all producers except sorghum producers where losses could be about $1.00 per acre. These losses represent minor impacts to the farmers using captan treated seed. The range of estimated losses are somewhat misleading since captan is applied largely by seed suppliers who use captan for different types of seed rather than contending with varying use practices for several types of fungicides. This practice achieves cost savings for the seed suppliers since shifting from one fungicide to another in the treatment boxes would involve the costs of down time and cleaning treatment boxes which would be considerable to the seed treatment industry as a whole. Estimating the economic value of this convenience was beyond the scope of this analysis.

1. Corn

An estimated 676,000 pounds of captan are used annually to treat virtually all of the field corn and 75 percent of the sweet corn seed planted in the U.S. Thiram is the alternative currently registered which is most likely to be used if captan use were cancelled since it was the seed treatment of choice prior to the availability of captan. Even though

thiram has been implicated in human dermatitis problems, available information indicates it still would be the preferred alternative.

Thiram could be used to replace captan with an annual increased treatment cost of about $1.4 million or about $0.02 per acre planted. Virtually all of the seed is treated by the seed suppliers and the increased cost would be either borne by the seed suppliers or corn producers.

2. Cotton

Captan is currently used to treat about 80 percent of the seed planted on approximately 14 million acres of U.S. cotton. In addition, a relatively minor quantity of captan is applied to the soil as a supplementary treatment when cool wet conditions are present at planting. Captan is usually applied in combination with another fungicide, such as carboxin, chloroneb, or fenaminosulf to provide broader spectrum disease control.

All cottonseed used in the U.S. is treated with fungicides by seed companies as a measure to reduce the probability of disease. With good soil conditions, seed treatment will provide adequate protection. However, when the soil is cool and wet at planting a supplementary soil treatment is necessary to insure a good stand. The likely alternatives to captan are captafol, 2-(Thiocyanomethylthio)benzothiazole (TCMTB), and thiram. It is expected that any of these alternatives would be mixed, as is captan, with other fungicides such as carboxin, chloroneb, and fenaminosulf.

Based upon current recommendations of cotton producing state extension plant pathologists, as well as cost, the likely alternative if captan use is cancelled is thiram. Any change in yield or change in cost associated with this substitution should be negligible. PCNB plus 5-Ethoxy-3-trichloromethyl-1,2,4-thiadiazole (ETCMTD) mixtures are likely to substitute for captan as a supplementary soil treatment with the cost approximately equal to captan.

3. Sorghum

Captan is used to treat sorghum seed for planting about 10.4 million acres of sorghum. This represents about 94 percent of the U.S. sorghum acres planted.

Seed treatment with captan controls a wide range of seed and seedling diseases. Potential alternatives to captan include mancozeb, PCNB, TCMTB, and thiram. Of these fungicides, thiram is the most likely alternative to be used in place of captan.

The annual cost of treatment would increase by about $51,000 with thiram or about $0.02 per acre. With the use of

thiram there would be a 0.1 percent decrease in yield on those acres currently treated with captan. This would result in an annual loss of about $1.9 million with producers bearing about $1.4 million of the loss and consumers bearing the remaining $500,000.

4. Soybeans

Captan is used to treat enough soybean seed to plant about 20 percent (about 14.3 million acres) of the U.S. soybean acreage. Captan is used as a control for various seed decay and seedling blight organisms. Potential alternatives to captan include maneb, PCNB with ETCMTD, carboxin with thiram, and thiram.

It was estimated that the annual costs of seed and seedling disease control would decrease by $6.2 million or increase by $3.4 million depending on the combination of alternatives adopted. No changes in crop yield or quality are expected. The per acre impact ranges from an increase in profits of $0.40 to a decrease of $0.24 which are expected to have negligible effects on farm management decisions. In the absence of any significant increase or geographical shifts in soybean acres, it is unlikely that any of the expected changes would be shifted to consumers.

5. Peanuts

Captan is applied to about 56 percent of the U.S. peanut seed as a control of seed and seedling diseases of peanuts. Captan is usually combined with other chemicals for application as a seed protectant. Potential alternatives to captan include DCNA, captafol, carboxin, and thiram. At least one of the alternatives could be used to replace captan without a reduction in yield.

It was estimated that a loss of captan would result in increased costs of production of about $146,000 annually. Since this amounts to about a $0.19 per acre increase in disease control costs, it is unlikely that any of the increased costs would be shifted to consumers.

6. Rice

Captan is used to treat about 37 percent of the rice seed used in California. This represents about 309,000 acres of rice or about 10 percent of the rice acres harvested in the U.S. Captan is used as a treatment for various seed and seedling disease causing organisms. Potential alternatives to captan include captafol, carboxin with thiram, cupric hydroxide, mancozeb, PCNB, TCMTB, and thiram.

If captan use is cancelled, growers now planting rice treated with captan would shift to captafol without any yield

impacts. Fungicide costs would increase by about $35,000 annually or about $0.11 per acre. It is expected that the producer would absorb these cost increases without any impact on the consumer.

7. Small Grains

Captan is registered for use on barley, oats, rye and wheat for the control of a variety of seed and seedling diseases as well as smut. It is estimated that about 2.8 million acres of these small grains are planted annually with captan treated seed; this represents 2 to 5 percent of the U.S. acreage for these crops.

With a loss of captan some combination of carboxin, maneb, thiram, TCMTB, maneb, hexachlorobenzene, PCNB, and ETCMTD would be used with annual treatment costs increasing by about $391,000 with no change in yields. On an individual crop basis, per acre cost changes would range from a decrease of $0.06 for rye to an increase of $0.14 for wheat. It is expected that the producers of these crops would absorb the cost changes with no impacts on the consumer.

8. Potatoes

Captan is registered for use on potato seed pieces to prevent infection of seed piece and of emerging seedlings. It is estimated that 377,000 or 27 percent of the commercial potato acreage is planted with captan treated seed pieces. Potential alternatives to captan include maneb, thiabendazole, ferbam, zineb, and metiram.

Maneb and mancozeb could be used to replace captan with a decrease in the cost of seed treatment ranging from $192,000 to $532,000 without any yield impacts. It is expected that potato producers would absorb these cost changes with no impact on the consumer.

9. Vegetables

Captan is also used on a variety of vegetable seeds for control of various disease causing organisms. The principle seeds treated are peas and beans. Alternatives available include thiram and fenaminosulf, which can be applied without any yield reductions.

Since about 72 percent of U.S. acreage of these crops is planted with captan treated seed, part of the annual $1.5 million potential increase in costs could be passed on to the consumer but data were not available to estimate the magnitude. Regardless of the portion of producer impact that is passed on to the consumer, the impact on the consumer would be negligible.

D. OTHER SITES

1. Home Gardens

About 100,000 pounds a.i. of captan are used annually by home gardeners on a variety of sites ranging from ornamentals to fruits and vegetables. Registered alternatives include benomyl, maneb, zineb, lime sulfur, bordeaux mixture, analazine, chlorothalonil, and folpet. Data are not available to estimate the effectiveness of captan in the home garden setting. However, data available for the commercial fruit, turf, and vegetable sections indicate alternatives could be employed with only relatively minor yield losses. There was no attempt to estimate the magnitude of impacts on home gardens since data were not available for homeowner use sites.

2. Forest Nurseries

Captan is registered for control of damping-off diseases in forest nurseries. Potential alternatives to captan include thiram, dazomet, TCMTB and ETCMTD plus thiophanate methyl. Available data indicate that alternatives will provide control of damping-off that is equivalent to captan. It is estimated that captan is annually used to treat approximately 1,250 acres, which represents about 8 percent of the U.S. forest nursery acreage.

Per acre control costs for alternatives range from a decrease of $124 per acre with TCMTB to an increase of $1,246 with thiram. This indicates that a shift to alternative controls could result in annual impacts ranging from a decrease in disease control costs of $155,000 to an increase of $1,557,000 depending on the combination of alternatives selected. Regardless of a gain or loss, the expected impact is negligible.

3. Turf

Captan is used on turf for control of several diseases. It is estimated that about 5,000 acres of turf are treated with captan on an annual basis. This represents less than one percent of the estimated 14 to 54 million acres of turf in the U.S. Thiram is the only alternative which provides control of a comparable range of diseases. Use of thiram would result in an annual increase in total disease control cost of about $28,000 or about $5.60 per acre which would be a minor impact.

4. Ornamentals

Captan is also used on a wide range of ornamentals for control of a large number of diseases. Although captan is registered for use on many plant/pest sites, in a number of cases other chemicals are preferred to captan. The principal uses of captan are for control of certain diseases in carnations,

control of corm rot on gladiolus, and control of selected diseases on field grown roses.

Current indications are that 45,000 to 50,000 pounds a.i. of captan are used on ornamentals. Benomyl and thiophanate methyl are the likely alternatives to captan on carnations. Neither of these alternatives can be used alone for an extended period of time due to development of disease resistance build up. Therefore, in the absence of additional alternatives it is expected that the carnation cutting production industry would be forced out of business as disease resistance increased to the remaining fungicides.

Thiabendazole is used extensively to control corm rot on gladiolus and would provide control equal to captan.

Benomyl, triforine, chlorothalonil, ferbam, zineb, and folpet provide alternative control of various rose diseases. Benomyl, chlorothalonil, and zineb providing equal control.

It has been estimated that the domestic carnation cutting producing industry (plants produced for flower growers) would be unable to continue to compete with imported cuttings if captan were cancelled. This would result in a short term annual loss of about $6,000,000 which would decrease as an alternative use is found for the resources currently devoted to carnation cutting production.

If the domestic carnation cutting production industry managed to survive the loss of captan, carnation cut flower growers would experience a 33 percent loss of plantings due to increased disease pressure. This could result in increased replanting costs of about $12.5 million.

The loss of captan for gladiolus corm treatment would result in cost of control increases of about $40,000 and on roses would result in cost of control increases of about $96,000.

It appears likely that the carnation cut flower industry would pass a significant portion of the increased costs to consumers in the form of short run higher prices. The minor production cost impacts on gladiolus and rose producers would not be expected to cause any consumer impacts.

E. NON-AGRICULTURAL USES

As discussed in Section II.C.2, there are several "non-agricultural" uses of captan as a biocide in plastics, adhesives, paints, and cosmetics. The latter is regulated by the Food and Drug Administration. Alternatives to captan for these uses exist and are summarized below (Pelletier, 1985). Though economic assessments of these uses have not been

conducted, numerous alternatives are registered for each use; however, there are no registered alternatives for dog and cat shampoos. The only alternative for captan in soaps is 4-chloro-3,5-xylenol. Listed below are the registered alternatives for captan for use in oil-based paints, plastics, and wallpaper flour adhesives.

Oil - (solvent) based paints

folpet
chlorathalonil
3-iodo-2-propynylbutyl carbamate pentachlorophenol
barium metaborate
trans-1,2 bis (propylsulfonyl) ethene
2,3,5,6 tetrachloro-4-methylsulfonyl pyridine
tribulytin salicylate
thiabendazole
2-n-octyl-4-isothiazolin-3-one

Plastics

folpet
10, 10' oxybisphenoxyarsine
copper-8-quinolinolate
diphenylstibine 2-ethylhexoate
2-n-octyl-4-isothiazolin-3-one
4-chloro-3,5-xylenol
2,3,5,6-tetrachloro-4-methylsulfonyl-pyridine
tributytin monopropylene glycol maleate
tripropytin methacrylate

Wallpaper Flour Adhesive

sodium o-phenylphenate tetrahydrate
1-(3-chloroallyl) 3,5,7-triaza-1-azoniaadamatane chloride
sodium pentachlorophenate
6-acetoxy- 2,4-dimethyl-m-dioxane
thiabendazole
chlorathalonil

IV. REGULATORY OPTIONS AND RISK BENEFIT ANALYSIS

A. INTRODUCTION

As previously explained, FIFRA requires the Agency to weigh the risks against the benefits for each use of a pesticide in order to determine whether continued registration would cause unreasonable adverse effects on the environment. In Chapters II and III, the risks posed by exposure to captan and the benefits derived from its registered uses were discussed. To determine whether continued registration of captan is appropriate, the Agency has identified a number of regulatory options, and has evaluated each option for its impacts on both risks and benefits.

In addition, the Agency has identified registered alternative pesticides for the various uses of captan. The general risks of alternative pesticides have been summarized based on the available data.

This section identifies the regulatory options available to the Agency to reduce the risks from the registered uses of captan. Each option has been evaluated for its impact on the risks and benefits of the registered uses of captan and the most appropriate regulatory options have been proposed.

B. RISK CONCLUSIONS

Exposure to captan can occur through application of the pesticide to agricultural crops, harvesting the crops, and eating foods containing residues of captan. Exposure can also occur from non-agricultural application of the pesticide (e.g., in paints, textiles) and by handling the end product to which captan has been added. In these ways, the entire U.S. population may be exposed to captan residues from agricultural and non-agricultural uses. These exposures and associated risks were discussed in detail in Sections II.C. and II.D. of this document.

1. Oncogenicity

As indicated in the Captan PD 1, the 1977 report by NCI showed a statistically significant dose related increase in adenocarcinomas and adenomatous polyps in B6C3F1 mice fed captan in their diet over 96 weeks. To determine whether the NCI results were accurate and to determine whether a threshold might exist for tumor development, Chevron performed a High Dose Study (HDS) (Chevron, 1981) and a Low Dose Study (LDS) (Chevron, 1983) which showed that adenocarcinomas developed in the gastro-intestinal tract in male and female mice. In addition, Stauffer Chemical Co. performed a chronic feeding study in Osborne-Mendel rats (Stauffer, 1982). The results showed a statistically significant increase in kidney tumors in male rats. Using data from the two mouse studies and the

rat study, the Agency calculated the Q_1^* (potency factor). This potency factor derived from a linearized multistage risk model and estimate of exposure were then used to estimate the upper limit, lifetime probability of excess oncogenic risk to humans. The specific risk estimates for oncogenicity were presented in Sections II.D.3 and II.D.4 and include both agricultural and non-agricultural risks to workers or users of end-products treated with captan.

2. Mutagenicity

As previously discussed in Section II.E, captan has been shown to be mutagenic in in vitro experiments in lower organisms, but the results were negative in the in vivo heritable translocation test. The Agency has concluded that captan is either non-mutagenic in vivo or possesses such a low mutagenic capacity in the in vivo assays used for quantitative heritable mutagenic activity that it is not possible to detect mutagenic activity. Although captan may be able to cause somatic mutational events and may, therefore, have an oncogenic problem, the risk of heritable mutagenicity for humans is low or nonexistent and does not warrant further testing at this time.

3. Reproduction

Sections II.B and II.G presented the Agency's concerns regarding reproductive effects. The Agency is concerned that the theoretical maximum residue concentration (TMRC) is 163% of the allowable daily intake (ADI); thus, there is an inadequate margin of safety between the no-observable-effect-level (NOEL) for toxic effects in reproduction studies and levels of captan to which people may be exposed through their diet. The TMRC was based on the tolerances; actual residue concentrations may be lower, but the data are not available to make such estimates. When registrants submit the required additional data on captan residues the Agency will recalculate the exposure and tolerances will be reassessed. Until such data are submitted, however, the Agency will base its regulatory proposals on tolerances.

4. Teratology

Section II.B presented information on teratogenic/feto-toxic effects of captan. Laboratory animals exhibited feto-toxic effects such as reduction in fetal weight and decrease in number of viable fetuses as well as teratogenic effects (e.g., exencephaly, fused ribs, and microphthalmia). Thus, captan may have the ability to produce fetal abnormalities. However, the risk assessment indicated that dietary exposure does not present a risk of concern (because the lowest margin of safety is 828). The Margins of Safety were calculated from a NOEL derived from a study in hamsters by Robens (1970). Because of omissions and/or inconsistencies in tabular data

and because statistical analyses were not performed in this study, the Agency is requiring registrants to perform another teratology study in hamsters to evaluate these effects more definitively.

5. Metabolism

The Agency is concerned about THPI, a plant and animal metabolite of captan, because this might cause tumors in laboratory animals. Current tolerances do not include THPI and therefore the dietary exposure may be understated. Therefore, since the Agency does not have sufficient data on residues of THPI to perform a risk assessment, such data will be requested pursuant to FIFRA 3(c)(2)(B). When data are submitted, the tolerances will be reassessed.

6. Ecological Effects

Although captan is acutely toxic to fish, the Agency does not expect use of captan to cause toxic effects in non-target aquatic species. There are no aquatic uses for captan and no significant leaching or runoff is expected. Captan is relatively non-toxic to birds and should pose no hazard to honeybees or predaceous mites. Thus, captan does not meet the Agency's risk criteria for ecological effects.

7. Risks From Chemical Alternatives to Captan

The chemical alternatives to captan were listed in Section III (Benefits Analysis) of this document. The Agency has information on the oncogenicity, mutagenicity, reproductive effects, and teratogenicity/fetotoxic effects for many of these chemicals. Table 1 summarizes these effects. For many of the chemicals the data base is incomplete. Without a complete data base, it is not possible at the present time to judge the relative toxicities of the alternatives as compared to captan. These data will be obtained as part of the Agency's Registration Standards process.

As indicated in Table 1, the Agency has initiated or completed Special Reviews and Registration Standards on a number of the alternative fungicides, and is also planning on examining the others in the future. As a result of these reviews, the Agency has made regulatory decisions on a number of fungicides. In cases where there were potential unreasonable adverse effects, the Agency took actions to reduce risks; where data were invalid or lacking, the Agency has required additional data pursuant to FIFRA 3(c)(2)(B). As these data are received and evaluated, the Agency will be better able to make regulatory decisions on each of the fungicides.

Table 2 compares the ecological effects for aquatic and avian toxicity of captan with that of the chemical alternatives. The toxic effects associated with exposure of

Table 1 - Summary of Effects of Captan Alternatives

FUNGICIDE	ONCO	TERATO	REPRO	MUTA	REGULATORY STATUS
benomyl	+	+	+	+	SR completed 10/82, RS - FY 86
biphenyl	?	?	?	?	
captafol	+	+	+	+	SR started 12/84
chlorothalonil	+	-	+	-	RS completed 1/81
coppers	?	?	?	?	
dichlone	?	?	?	?	RS completed 1/81
dichloran	-	-	-	?	
dinocap	?	+	?	?	SR started 1/85
dinoseb	?	?	?	?	
fenarimol	+	+	+	-	
ferbam	?	?	?	?	
folpet	1/	-	?	+	
mancozeb	+	+	+	+	SR completed 10/82, RS - FY 86
maneb	+	+	?	+	SR completed 10/82, RS - FY 86
metalaxyl	?	?	?	?	RS completed 8/81
methyl chloroform	?	?	?	?	
methylene chloride	?	?	?	?	
metiram	+	+	?	+	SR completed 10/82, RS - FY 86
o-phenylphenol	+	-	?	-	DCI sent out 10/84
sodium arsenite	?	?	?	?	
sodium dimethyl-dithiocarbamate	?	?	?	?	
sodium phenylphenate	+	?	?	-	
tetraiodoethylene	?	?	?	?	
thiabendazole	-	-	+	-	
thiophenate-methyl	?	?	?	?	SR completed 10/82, RS - FY 85
thiram	?	?	?	?	
triadimefon	?	+	+	-	
triforine	-	-	?	?	
triphenytin-hydroxide	?	+	?	?	
2-aminobutane	?	?	?	?	
vinclozolin	?	+	-	?	
zineb	+	+	?	+	SR completed 10/82, RS - FY 86

+ = positive effects
- = no effects
? = data gap or not known at this time
SR = Special Review (RPAR)
RS = Registration Standard
DCI = Data Call-In Letter

1/ Oncogenic risk assessment in progress

Table 2 - Summary of Ecological Effects of Captan Alternatives

Alternative	Aquatic Toxicity	Avian Toxicity
2-aminobutane	<	ND
Sodium arsenate	<	>
Dichloran	<	=
Ferbam	>	=
Methyl chloroform	<	=
Triforine	<	=
Methylene chloride	ND	ND
Tetraiodoethylene	ND	ND
Triadimefon	<	>
Vinclozolin	<	>
Triphenyltin-hydroxide	>	>
Thiophanate methyl	>	>
Metalaxyl	<	>
Fenarimol	<	<

= equal toxicity relative to captan
> greater " " " "
< less " " " "

aquatic or avian species to alternatives are greater than, equal to, or less than the toxicity associated with captan.

C. BENEFIT CONCLUSIONS

The benefits of captan were assessed in terms of economic impacts which would result if its uses were cancelled and users were forced to employ available alternatives. As detailed in Section III, should captan use be cancelled, moderate economic impacts would fall on the ornamental plant industry due to the loss of captan use on carnations ($6 to $12.6 million). Moderate impacts are also anticipated to occur for apples ($0.9 - $3.3 million), almonds ($1.4 million), bushberries ($3.5 - $4.0 million), strawberries ($5.9 million), peaches ($2.3 - $5.0 million), apricots ($0.4 - $0.7 million), nectarines ($0.7 million), and seed treatments (up to $9.2 million for all seed treatments). Although the impact would be moderate to users of treated seed in aggregate, the per acre impact for seed treatments would be minor.

Although not quantified, cancellation of home garden uses could result in an increase in the cost of disease control since several more expensive fungicides would be used to replace the various home garden uses of captan.

For all other uses of captan, the impacts would be minor to insignificant for growers and consumers. The Agency does not expect any measurable impact on nationwide production or prices of food, or any other facet of the agricultural economy.

Registered alternatives exist for almost all uses of captan but in many cases the alternatives are not as effective. For the carnation plant industry it was predicted that resistance would build within two years to the available alternatives.

D. DEVELOPMENT OF REGULATORY OPTIONS

There are three basic options for regulating all pesticides:

Option 1 - Continuation of Registration without Changes

Option 2 - Continuation of Registration with Modifications to the Terms and Conditions of Registration

Option 3 - Cancellation of Registration

The two extreme options, Option 1, Continuation of Registration without Change and Option 3, Cancellation of Registration, are at the opposite ends of the risk/benefit spectrum. Adoption of Option 1 would be appropriate when the Agency has concluded that the level of risk is acceptable in light of the pesticide's benefits and that further risk reduction measures are not necessary to assure that the use

of the pesticide meets the statutory standard for continued registration.

Adoption of Option 3, cancellation, would be appropriate when the Agency has concluded that the risks from a use outweigh the benefits of that use, and that these risks cannot be mitigated to an acceptable level, in light of the benefits, by any other measures short of cancellation. Cancellation may affect all uses of a compound, only specific uses or specific formulations, or specific application methods.

Option 2 is appropriate when the risks of a pesticide use can be reduced to a level where the benefits of use outweigh the risks. This risk reduction is accomplished by modifying the terms and conditions of the pesticide's registration. These modifications, which are expressed through the pesticide's labeling are, for the most part, changes in the way the pesticide is used. These changes are designed to reduce exposure to the pesticide and thereby reduce or eliminate the risk from the pesticide. Risk reduction measures were considered and evaluated for their potential effectiveness and feasibility.

1. Measures to Reduce Dietary Exposure

Amounts of pesticide residues on food crops are affected by quantity of active ingredient used, the solvents used for dilution, mode and schedule of application, preharvest interval, and soil and weather conditions. Several measures were considered as means by which dietary exposure to captan through residues on food crops might be reduced.

a. Preharvest Intervals

Dietary exposure due to captan residues on food crops might be reduced if preharvest intervals were extended. The preharvest interval is the number of days that must elapse between the final application of the fungicide and actual harvest. Lengthening this interval may allow time for dissipation of residues before crops are harvested. Additionally, lengthening the preharvest interval can serve as a means of lowering tolerances. However, extending the preharvest interval cannot be evaluated in the absence of dietary exposure/residue data that would enable the Agency to determine the extent to which dietary exposure might be reduced. Until the necessary data become available, an informed risk/benefit analysis of this particular option is not possible.

b. Modify Application Practices

There is the possibility that dietary exposure due to captan residues on food crops could be reduced if current application practices were modified. Specifically, three possibilities have been considered: (1) reducing the amount

of active ingredient in the formulations, (2) reducing the amount of formulation applied per season, and (3) reducing the amount of active ingredient applied per acre. These modified application practices, like increasing the preharvest intervals, might enable tolerances to be lowered. There is also the possibility that prohibiting post-harvest application could reduce the captan residues, but since the tolerances established do not distinguish between pre- and post-harvest residues, the Agency cannot determine the extent of risk reduction if post-harvest applications were prohibited.

At this time, modified application practices cannot be pursued as a viable option in the absence of dietary exposure/residue data that would enable the Agency to determine the extent to which dietary exposure might be reduced. Until the necessary data become available, an informed risk/benefit analysis of this particular option is not possible.

c. Reassess Tolerances for Captan Residues

The Agency's risk assessment for captan focused primarily on dietary exposure to captan as a result of various food and feed uses of captan. For purposes of calculating worst-case dietary risk, the Agency assumed that captan residues are present at current tolerance levels. Worst-case dietary exposure could possibly be reduced if captan tolerances were reassessed and lowered.

However, the data base to support captan tolerances is not complete. Accordingly, the Agency is requiring residue data pursuant to FIFRA 3(c)(2)(B). After the required data are received and evaluated, the tolerances can be reassessed. However, until the necessary tolerance/dietary exposure data become available, the Agency will use the worst-case dietary risk estimates as a basis to propose regulatory action.

d. Cancel Food Crops with Highest Dietary Exposure

An option to cancel only the highest risk food crop uses (i.e., crops with oncogenicity risks of 10^{-4} to 10^{-5} (B2)) was also examined. However, this option would reduce total dietary risks by less than an order of magnitude. The risks would still be of the order of 10^{-4} (B2). This dietary risk is considered to be too high in light of the moderate to minor benefits to food crops.

2. Measures to Reduce Exposure to Applicators, Mixer/Loaders, and Fieldworkers

The potential risks to person mixing or loading captan formulations, applying the pesticide to crops, and working in the fields treated with the pesticide were calculated. The specific risk reduction measures which the Agency has considered are:

a. Protective Clothing

Dermal and inhalation exposure to captan can occur during mixing, loading, maintenance of application equipment, during application, and at the time fieldworkers enter treated fields to weed and harvest.

Protective clothing, comprised of gloves and dust masks, is expected to reduce risk by 80%. Respirators are expected to reduce inhalation exposure by 90%. If implemented, protective clothing or equipment requirements would have a minimal impact on economic benefits.

b. Reentry Interval

Establishing a reentry interval would allow time for further breakdown of captan residues. Presently workers may reenter fields when the formulation applied to crops has dried. However, the Agency has no data on deterioration of captan or THPI over time and thus cannot propose a specific reentry interval.

3. Measures to Reduce End-Use Exposure

The potential risks to persons using end-use products (e.g., plastics, adhesives, paints, etc.) containing captan may be reduced by modification to the concentration used and by use of protective clothing. The risks to people in nursing homes and hospitals using mattresses and pillows containing captan as a preservative is reduced by the normal practice of using sheets and pillow cases or other coverings.

a. Modification of Concentration

The risks to users of products containing captan may be reduced by decreasing the amount of active ingredient in the mixture. It is possible that reducing the amount of captan in plastics, adhesives, paints, cosmetics, and shampoos might not significantly alter its efficacy, but would decrease risks. However, the Agency has no data on which to propose any reduction in concentration.

b. Protective Clothing

If protective gloves are worn for certain uses of end-products, the risk is expected to be reduced by 80%. If implemented, a protective glove requirement would have minimal impacts on economic benefits. When coverings are used for mattresses and pillows, the risk is reduced significantly.

E. RISK/BENEFIT ANALYSIS OF REGULATORY OPTIONS

1. Agricultural Uses

a. Foliar and Post-Harvest Use

If the registrations of captan products for use on food and feed crops were continued without restriction (Option 1), the total dietary cancer risk would be estimated to be 10^{-3} to 10^{-4} (B2). The benefits (estimated to be at $12 to $31 million) would remain unaffected. The estimated total risk was based on the TMRC in the absence of residue data to the contrary. It was calculated assuming an individual consumed a normal diet containing food items treated with captan.

The Agency assumed that captan is present on food crops at the level of existing tolerances because it is the level which could legally be present and because the existing residue data are inadequate for risk assessment purposes. The residues are probably not as high as the tolerance level, but they are probably higher than the residues shown for the selected crops analyzed in the Market Basket Surveys as shown shown in Section II.C.1.d. of this document. Therefore, in the absence of adequate residue data, the Agency will base its regulatory proposal for agricultural uses of captan on dietary risks estimated from exposures based on tolerances.

Because of lack of data, the Agency does not know whether amending the terms and conditions of registration (Option 2) by extending the pre-harvest interval, modifying the application practices, or reducing the tolerances on crops would reduce the total dietary risk to any significant extent.

If the registrations of captan products for food uses were cancelled (Option 3), all risks to persons consuming captan treated crops would be eliminated. The cancellation of these registrations would have a $12 to $31 million impact. However, these impacts are considered to be moderate to minor because these costs are expected to be reasonably absorbed by growers and consumers; moreover, these costs are low in relation to the total value of each affected crop.

Based on the significant cancer risks and moderate to minor benefits associated with the food uses of captan, the Agency has determined that the risks outweigh the benefits for Options 1 and 2. There is a possibility that actual residues consumed may be substantially lower than tolerance levels, and the Agency is requiring data to refine the risk assessment. These data include residues on processed crops found before and after washing, after peeling, and after processing or cooking. Data on THPI residues will also be required. Validation data for the analytical methodology used by the registrants for the market basket survey will be required. Poultry and cattle feeding studies will be required

because residues for milk, eggs, and tissues are lacking. Residue data for food crops will be required for captan as well as THPI. Residue data for captan and THPI is required in plants which have developed from seeds previously treated with captan. The data which are needed for regulatory decision making will be submitted by the registrants and reviewed by the Agency before Position Document 4 is issued. The Agency encourages all interested parties to submit data on ways in which exposure to captan might be reduced so that the Agency will be able to consider all possible risk reduction methods before making a final regulatory decision in the Position Document 4.

In the final decision, the Agency will retain any use where data are submitted that demonstrate that actual residues are sufficiently lower than current tolerances or that modifications to application practices will sufficiently reduce dietary risk. However, until the data are submitted, the Agency proposes to cancel the use of captan products for use on all food crops in order to eliminate unreasonable adverse effects from exposure to captan through the diet. The projected economic impact could be up to $31 million based on yield losses and increased cost of alternatives.

b. Seed Treatment Uses

Captan was registered for use on seeds as a non-food use and residue data were not required. The Agency now considers seed treatment to be a food use and to continue this use the Agency will require submission of data to establish tolerances for the plants which grow from the seeds and which, therefore, may contain residues of captan and/or its metabolites. Although the Agency does not have these data, it is assuming, for the present, that residues resulting from this use would be present at or below limits of detection, and that the dietary risks to humans would be insignificant. Seed treatment uses will be retained until the required data are submitted and evaluated to determine whether there are any risks of concern from this use.

c. Detreated Seed Use

A tolerance was established for detreated corn seed fed to cattle and hogs on November 6, 1981 (21 CFR 561.65). The Agency determined that alkaline washing or roasting of the treated seeds would decrease the captan residues below 100 ppm. Feeding studies showed that there would be no captan residues in these animals if a 14-day pre-slaughter interval were adopted. Therefore, based on the benefits and negligible human dietary exposure, the Agency has decided to continue to allow feeding of detreated seed corn to cattle and hogs 14 days before slaughter if the residues are less than 100 ppm.

2. Non-Food Uses (Ornamentals)

a. Applicators

The potential oncogenic risk to persons applying captan to non-food crops was estimated to be in the range of 10^{-5} to 10^{-6} (B2). The Agency has concluded that these risks must be reduced by modifying the terms and conditions of registration. Therefore, the Agency proposes that labels be amended to require applicators to wear impermeable gloves and dust masks when applying captan to non-food crops (e.g., ornamentals). The risks to these workers would be lowered by 80% to about 10^{-6} (B2).

b. Mixer/Loaders

If the labels for captan formulations did not contain further warnings for mixer/loaders (Option 1), the risk to these workers range from 10^{-5} to 10^{-6} (B2). The Agency has found that these risks do not warrant cancellation, but believes that the risks must be reduced by modifying the terms and conditions of registration. The Agency proposes that the labels be amended to include a requirement that these workers must wear dust masks and impermeable gloves when mixing or loading captan formulations. This would reduce total exposure by 80%, thus reducing the risk to about 10^{-6} (B2).

c. Fieldworkers

Exposure estimates developed for fieldworkers (surrogate data from harvesters and weedpickers in strawberry fields) indicate that there is significant dermal exposure to these workers. Under Option 1, no restrictions, the risks range from 10^{-4} to 10^{-6} (B2). These risks would be representative for all workers in fields or nurseries with ornamentals treated with captan formulations. The Agency has found that these risks are not high enough to warrant cancellation (Option 3), but believes that the risks must be reduced by modifying the terms and conditions of registration. The Agency proposes that the labels be amended to include a requirement that these workers must wear water resistant gloves such as leather or other synthetic materials when working in fields or in nurseries in which the ornamentals have been treated with captan formulations. The risks to these workers would then be lowered by 90% to an upper limit of 10^{-6} (B2).

3. Non-Agricultural Uses

a. Applicators

The potential oncogenic risks to persons incorporating captan into plastics, adhesives, paints, and cosmetics were calculated. The risks were considered negligible for applicators of captan to plastics, paints, and cosmetics as long as they

wear protective clothing and a respirator or dust masks (cosmetics). The upper bound estimates of risks to applicators for adhesives were 10^{-5} (B2). Because these risks may be reduced significantly (by 80% to 90%) by wearing protective clothing or equipment, the Agency proposes that applicators wear gloves, protective clothing, and respirators (dust masks for cosmetic applicators) at all phases of the application process for all non-agricultural uses.

b. End-Uses

The potential oncogenic risk to users of end products containing captan were calculated.

1) Plastics

For exposure to plastics containing captan, the risks were calculated to be negligible. For exposure to mattresses and pillows containing captan the upper bound estimate of risk is 10^{-5} to 10^{-6} (B2). However, the Agency will not propose any regulatory action for this use since coverings over the captan-treated mattresses and pillows are used as a normal practice and are assumed to reduce risk by at least an order of magnitude to a range of 10^{-6} to 10^{-7} (B2).

2) Adhesives

For exposure to adhesives containing captan used in the home, the upper bound estimates of risks were calculated to be 10^{-6} to 10^{-7} (B2). For professional use the risk was calculated to be 10^{-5} (B2). These risks are considered by the Agency to be outweighed by the benefits of use of captan. Thus, the Agency does not propose to take any regulatory action to modify the terms and conditions of registration of adhesive products containing captan.

3) Paints

For exposure to paints containing captan, the upper bound estimates of potential oncogenic risks to users were calculated to be 10^{-5} (B2) for oil-based paints and 10^{-6} (B2) for water-based paints. The Agency has found that these risks are not high enough to warrant cancellation, but believes the risks can be reduced by modifying the terms and conditions of registration. The Agency proposes that labels be amended to include a requirement that impermeable gloves must be worn when applying oil-based paints for home or professional use. This would reduce risks by 80%, thus reducing the risks to levels where they are outweighed by the benefits.

4) Shampoos

For dog and cat shampoos or powders containing captan, the upper bound estimate of risk to humans is 10^{-4} to 10^{-5} (B2) for

exposure due to washing pets. Since there are no registered alternatives for this use, the Agency concludes that the benefits outweigh the risks of these uses but only if impermeable gloves are worn during exposure. The use of impermeable gloves will reduce the upper bound estimate of risk by an order of magnitude to a range of 10^{-5} to 10^{-6} (B2).

For use of the sanitizing deodorant powdered hand soap containing 0.87% captan (Vancide 89) as an antimicrobial agent, the upper bound estimate of human potential oncogenic risk is 10^{-5} to 10^{-6} (B2). This figure is based on a worst-case exposure scenario; the Agency expects the actual risks to be lower because the hands are rinsed off right away. In addition, because numerous bacteria and fungi may degrade the product and because the presence of pathogenic bacteria could lead to infections, the Agency concludes that the benefits of this minor use of captan outweigh the risks and will not propose any regulatory action.

5) Other End-Use Products

For exposure to surface sprays and pet powders containing captan, the upper bound estimates of risks to humans are 10^{-9} (B2) and 10^{-8} (B2), respectively. The risks from exposure to packing boxes containing captan is assumed to be negligible. The Agency concludes that the benefits of use outweigh the risks in these situations and will not propose any regulatory action.

F. SUMMARY OF PROPOSED DECISION

1. Agricultural Uses

a. Foliar and Post-Harvest Use

Propose to cancel the use of captan products for the use on all food crops, but require additional residue data to support tolerances and to determine actual food residues. However, in the final decision, the Agency will retain any use where data are submitted that demonstrate that actual residues are sufficiently lower than current tolerances or that modifications to application practices will sufficiently reduce dietary risk.

b. Seed Treatment Uses

Seed treatment uses will be retained until additional data are submitted to enable the Agency to assess the risks.

c. Detreated Seed Use

Continue the use of detreated seed for feeding to cattle and hogs.

2. Non-Food Uses (Ornamentals)

a. Foliar and Post-Harvest Use

Continue the use of captan products on non-food crops.

b. Applicators

Labels must be amended to include a requirement that workers must wear impermeable gloves and dust masks when applying captan formulations.

c. Mixer/Loaders

Labels must be amended to include a requirement that workers wear dust masks and impermeable gloves when mixing or loading captan formulations.

d. Fieldworkers

Labels must be amended to include a requirement that workers wear water-resistant gloves (such as leather or synthetic materials) when working in fields or nurseries in which the crops had been treated with captan formulations. This regulatory proposal applies only to non-food items such as ornamentals since the Agency is proposing to cancel registrations of captan for use on food crops.

3. Non-Agricultural Uses

a. Adhesives

1) Applicators

Labels must be amended to include a requirement that workers wear respirators, gloves, and protective clothing (such as long-sleeved shirts and trousers) at all phases of the application process, as is the usual industrial practice.

2) End-uses

No proposed action.

b. Plastics/Fabrics

1) Applicators

Labels must be amended to include a requirement that workers wear gloves, protective clothing (such as long-sleeved shirts and trousers), and respirators at all phases of the application process, as is the usual industrial practice.

2) End-uses

No proposed action.

c. Paints

1) Applicators

Labels must be amended to include a requirement that workers wear gloves, protective clothing (such as long-sleeved shirts and trousers), and respirators at all phases of the application process, as is the usual industrial practice.

2) End-uses

Labels must be amended to include a requirement that impermeable gloves be worn when applying oil-based paints for home or professional use.

d. Cosmetics (including animal shampoos and dusts)

1) Applicators

Labels must be amended to include a requirement that workers wear gloves, dust masks and protective clothing (such as long-sleeved shirts and trousers) at all phases of the application process, as is the usual industrial practice.

2) End-uses

Labels be amended to include a requirement that people must wear impermeable gloves when washing their pets with animal shampoos containing captan. No regulatory will be proposed for powdered hand soaps, surface sprays, or pet powders containing captan.

The Agency will transmit to the FDA for their evaluation exposure and risk data on other cosmetic uses of captan not regulated by the EPA.

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