AMITRAZ

RISK CHARACTERIZATION DOCUMENT

Volume 1

HEALTH ASSESSMENT SECTION

MEDICAL TOXICOLOGY BRANCH, DEPARTMENT PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

December 12, 1995

EXECUTIVE SUMMARY

A. INTRODUCTION

Prior to being sold or applied to crops in the state of California, pesticides must go through a comprehensive evaluation and registration process conducted by the Department of Pesticide Regulation (DPR). This process is performed subsequent to registration by the United States Environmental Protection Agency (U.S. EPA). The Medical Toxicology Branch of DPR is responsible for reviewing toxicology data for all new and existing pesticides. These reviews consider the adequacy of the tests and the potential for adverse health effects. Following an analysis of worker exposure (estimated by the Worker Health and Safety Branch of DPR) the Medical Toxicology Branch evaluates the pesticide's risk potential and generates a risk characterization document (RCD).

This document characterizes the risk associated with dietary and occupational exposure to amitraz, a formamidine compound with insecticidal and acaricidal activity. Amitraz is presently marketed in the United States by the Nor-Am Chemical Company and by the Upjohn Company. It is registered by the U.S. EPA and DPR for the control of ticks and lice on cattle and swine, ticks on dogs, and to control pear psylla and mites on pears. Amitraz is also registered by the U.S. EPA for the control of bollworm, tobacco budworm, pink boll worm, whitefly, and mites on cotton. The use of amitraz on cotton is being considered in a current section 3 registration petition to California. In addition, amitraz has been registered by the U.S. EPA for the control of mites that infect honey bees. While this registration has been voluntarily canceled, existing stocks can still be used. The use of amitraz with honey production has not been registered in California. It is, however, considered for this risk assessment, inasmuch as honey and beeswax can enter California from other states.

B. RISK ASSESSMENT PROCESS

The risk assessment process incorporates four aspects: hazard identification, dose-response evaluation, exposure assessment, and risk characterization.

Hazard identification entails review and evaluation of the toxicological properties of each pesticide. The dose-response assessment then considers the toxicological properties and estimates the amount that could potentially cause an adverse effect. The amount that will not result in an observable or measurable effect is the No-Observed-Effect Level (NOEL). A basic premise of toxicology is that at a high enough dose, virtually all substances will cause toxic manifestations. Chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals that require low or high dosages, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies that define the types of toxic effects that can be caused, and the exposure levels (doses) at which effects may be seen. State and federal testing requirements mandate that substances be tested in laboratory animals at doses high enough to

produce toxic effects, even if such testing involves chemical levels many times higher than those to which people might be exposed.

In addition to the intrinsic toxicological activity of the pesticide, the other parameters critical to determining risk potentials are the level, frequency and duration of exposure. The purpose of the exposure evaluation is to determine the potential amount of the pesticide likely to be delivered through occupational, or dietary routes on an acute or chronic basis.

The risk characterization then integrates the toxic effects observed in the laboratory studies, conducted with high dosages of pesticide, to potential human exposures to low dosages of pesticides in the diet or work place. The potential for possible non-oncogenic adverse health effects in human populations is generally expressed as the margin of safety, which is the ratio of the dosage that produced no effects in laboratory studies to the estimated dietary and work related dosage. For oncogenic effects, the probability of risk is calculated as the product of the cancer potency of the pesticide and the estimated human dosage.

C. TOXICOLOGY

A DPR review of the toxicology studies on the effects of amitraz has identified adverse responses in human and animal studies. Central nervous system (CNS) effects in humans and dogs have been detected within hours of amitraz exposure. The effects seen in humans included paleness, dry mouth, drowsiness, disorientation, light headed feeling, slurred speech, and loss of consciousness. Toxic effects associated with sub-chronic exposure were indicated in a variety of studies. The most prevalent effects included decreases in body weight gain and abnormal CNS responses. The toxic effects of chronic exposure to amitraz included CNS depression, depressed growth rate, a reduction in food intake, hyperplastic nodules, and hyperkeratosis of the forestomach. Chronic exposure to amitraz has also been associated with oncogenicity. An increase in lymphoreticular, liver, and lung tumors has been reported in mice. Animal studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Mutagenic potential was indicated for 2,4-dimethylaniline (an amitraz metabolite) in bacteria and mammalian cells grown *in vitro* while amitraz exhibited mutagenic potential only in mammalian cells. Genotoxic potential was equivocal in an in vivo assay. In the mouse dominant lethal assay, one study produced positive results while the other resulted in negative data. For all other tests, amitraz was considered negative for genotoxic potential.

D. EXPOSURE ANALYSIS

In estimating dietary exposure, amitraz residue values for all commodities except honey were based on field trials conducted by the registrant. Residue levels in honey were based on the U.S. EPA tolerances.

Estimated dosages of amitraz considered both dietary and occupation-related exposures. The primary occupation-related activities addressed in this document

included: potential exposure to mixer/loader/applicators and harvesters involved in the treatment of pears; potential exposure to mixer/loaders, applicators, flaggers, and field checkers involved in the treatment of cotton, and potential exposure to mixer/loader/applicators involved with the treatment of livestock. Absorbed dosage estimates were made for acute, seasonal, annual, and lifetime exposures.

E. RISK EVALUATION

On the basis of the indicated effects and estimated dosages, margins of safety, defined as the ratio of NOEL to the absorbed dosage, were calculated for both occupational and dietary exposures to amitraz.

In general, a margin of safety equal to or greater than 10 is considered adequate for the protection of human health when it is based on NOELs from human studies. When NOELs are based on non-human mammalian studies, an additional factor of 10 is generally used (i.e., MOS of 100). For amitraz, margins of safety for acute exposure were based on human data. Margins of safety for seasonal, annual, and life-time exposures, however, were based on NOELs from non-human mammalian data (i.e., a dog study for seasonal and a mouse study for annual and life-time exposures).

For occupational exposure, margins of safety for acute exposures to amitraz ranged from 3 to 7 for mixer/loader/applicators in pear orchards (5), pear harvesters (3), mixer/loaders involved with the aerial treatment of cotton (4), pilots (7) and flaggers (4). For all other job classifications evaluated, margins of safety for acute exposure to amitraz were greater than 10. For seasonal exposures, the calculated margin of safety for pear harvesters was 11. For all other job classifications evaluated, margins of safety for seasonal exposure to amitraz were at least 100. For chronic (annual) exposures, the calculated margin of safety for pear harvesters was 63. For all other job classifications evaluated, margins of safety for annual exposure to amitraz were greater than 100. For chronic (life-time) exposures, non-oncogenic margins of safety were all greater than 100.

For dietary exposure, the margin of safety for acute exposure to amitraz was 8 for children ages 1 to 6. For all other population subgroups, margins of safety were greater than 10.

For combined (occupational and dietary) exposure, margins of safety for acute exposures to amitraz ranged from 2 to 8 for mixer/loader/applicators in pear orchards (4), pear harvesters (2), mixer/loader/applicators involved with the ground treatment of cotton (8) mixer/loaders involved with the aerial treatment of cotton (3), pilots (6) and flaggers (4). For field checkers and workers involved with the treatment of livestock, margins of safety for acute exposure to amitraz were at least 10. For seasonal exposures, the calculated margin of safety for mixer/loader/applicators in pear orchards was 96. For pear harvesters the margin of safety was 11. For all other job classifications evaluated, margins of safety for seasonal exposure to amitraz were greater than 100. For chronic (annual) exposures, the calculated margin of safety for pear harvesters was 60. For all other job classifications evaluated, margins of safety

for annual exposure to amitraz were greater than 100. For chronic (life-time) exposures, non-oncogenic margins of safety were all greater than 100.

Cancer risk estimates for occupational exposure to amitraz related to its use on pears, cotton, or livestock, based on the maximum likelihood estimate (Q_1) of the potency slope, ranged from 1.6×10^{-7} to 6.0×10^{-5}. Cancer risk estimates, based on the upper bound (Q_1*) of the potency slope ranged from 3.0×10^{-7} to 1.1×10^{-4}. The occupation with the highest risk was pear harvesters.

Cancer risk estimates for dietary exposure to the U.S. population, based on Q_1 and the Q_1* were, 6.8×10^{-6} and 1.2×10^{-5}, respectively.

For combined occupational and dietary exposures, the calculated risk for agricultural workers using amitraz ranged from 6.9×10^{-6} to 6.7×10^{-5}, when based on the Q_1 . When based on the Q_1*, the cancer risk estimates ranged from 1.3×10^{-5} to 1.2×10^{-4}. The occupation with the highest risk was pear harvesters.

F. CONCLUSIONS

The toxicology data base for amitraz has indicated potential adverse effects in human and laboratory animal studies. Effects reported after acute exposure to the pesticide have generally been associated with the central nervous system. Studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Chronic exposure to amitraz has been associated with an increased incidence of oncogenicity in mice. The genotoxicity data base indicates that amitraz and 2-4-dimethylaniline (a primary plant metabolite and an intermediate mammalian metabolite of amitraz) have mutagenic potential.

Several occupational activities associated with the agricultural use of amitraz, and one population sub-group potentially exposed to amitraz through the diet, have margins of safety less then the values conventionally considered to be protective of human health. In these cases, mitigation should be considered to reduce potential exposure.

Cancer risk estimates for occupational exposures (including dietary) to amitraz through the use on pears, cotton, or livestock, and non-occupational exposures via consumption of commodities treated with amitraz, were between 1 and 12 in 100,000. For dietary exposure only, cancer risk estimates were between 7 and 12 in 1,000,000.

An additional assessment of acute risk potential based on U.S. EPA tolerances indicates that margins of safety based on current U.S. EPA set tolerance levels are less then the values conventionally considered to be protective of human health.

CONTRIBUTORS AND ACKNOWLEDGMENTS

Author:	Joseph P. Frank, D.Sc., Staff Toxicologist (Specialist) Health Assessment Section, Medical Toxicology Branch
Toxicology Reviews:	Joyce Gee, Ph.D., Senior Toxicologist SB-950 Data Review Section, Medical Toxicology Branch
	Ronald L. Morgan*, Ph.D., Staff Toxicologist (Specialist) Product Data Review Section, Medical Toxicology Branch
	Thomas B. Moore, Ph.D., Staff Toxicologist (Specialist) Product Data Review Section, Medical Toxicology Branch
	Harry F. Green, B.S., Associate Pesticide Review Scientist SB-950 Data Review Section, Medical Toxicology Branch
Dietary Exposure:	Wesley Carr, M.S., Associate Pesticide Review Scientist Health Assessment Section, Medical Toxicology Branch
Peer Review:	Earl F. Meierhenry, D.V.M., Ph.D., A.C.V.P., Staff Toxicologist (Specialist) Health Assessment Section, Medical Toxicology Branch
	Keith Pfeifer, Ph.D., D.A.B.T., Senior Toxicologist Health Assessment Section, Medical Toxicology Branch
	Jay Schreider, Ph.D., Primary State Toxicologist Medical Toxicology Branch, Medical Toxicology Branch

* Not currently employed by the State of California

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

TABLE OF CONTENTS

I. SUMMARY

A. INTRODUCTION

This document characterizes the potential risk associated with occupational and dietary exposure to the pesticide, amitraz. This assessment was performed under the provisions of the California Birth Defect Prevention Act (Senate Bill 950), and the Assembly Bill 2161 (sometimes referred to as the Food and Safety Act). Senate Bill 950 requires a scientific determination that use of a registered pesticide will not cause significant adverse health effects. Assembly Bill 2161 requires risk assessments on the dietary exposure to pesticides in both raw agricultural commodities and processed foods.

Amitraz is the common name for N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)-imino]-methyl]]-N-methylmethanimidamide. Amitraz is an insecticide/acaricide marketed in the United States by the Nor-Am Chemical Company as Mitac® EC (emulsifiable concentrate), Mitac® WP (wettable powder), Taktic®, , Preventic®, and Ovasyn®, and by the Upjohn Company as BAAM® EC and BAAM® 50W. The Mitac® products are registered to control pear psylla and mites on pears whereas Taktic® is registered to control ticks and lice on cattle and swine. Preventic® is used in dog collars and Ovasyn® is used on cotton. Ovasyn® is not currently registered in California, however, this product has been submitted to the state for a section 3 registration. Amitraz was also registered by the U.S. EPA for the control of mites that infect honey bees. While this registration has been voluntarily canceled, existing stocks can still be used. The use of amitraz with honey production has not been registered in California. It is, however, considered for this risk assessment, inasmuch as honey and beeswax can enter California from other states.

B. TOXICOLOGY

A DPR review of the toxicology studies on the effects of amitraz has identified adverse responses in human and animal studies. Central nervous system (CNS) effects in humans and dogs have been detected within hours of amitraz exposure. The effects seen in humans included paleness, dry mouth, drowsiness, disorientation, light headed feeling, slurred speech, and loss of consciousness. The acute no observed effect level (NOEL) used in this risk assessment was 0.125 mg/kg and was based on the indicated CNS response in humans. Toxic effects associated with sub-chronic exposure were indicated in a variety of studies. The most prevalent effects included decreased body weight changes and CNS depression. In a 90-day toxicity study conducted with dogs, a NOEL of 0.25 mg/kg/day was based on CNS depression and catarrhal conjuctivitis. The toxic effects of chronic exposure to amitraz included CNS depression (specific signs not reported), depressed growth rate, a reduction in food intake, hyperplastic nodules, and hyperkeratosis of the forestomach. The "CNS" effects were considered a response to acute exposure as they were observed 3 hours after dosing. On the basis of hyperplastic nodules in females and hyperkeratosis of the forestomach in males (in B6C3F1 mice), a LOEL of 2.3 mg/kg/day was established for chronic toxicity. An estimated NOEL of 0.23 mg/kg/day for non-oncogenic effects was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10 (U.S. EPA,

1987c). Chronic exposure to amitraz has also been associated with oncogenicity. An increase in lymphoreticular, liver, and lung tumors in CFLP mice has been reported. Hepatocellular tumors have also been associated with exposure to amitraz in B6C3F1 mice. Animal studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Genotoxic potential was indicated for 2,4-dimethylaniline (an amitraz metabolite) in bacteria (Ames test) and mammalian cells grown *in vitro* (L5178Y mouse lymphoma assay) while amitraz exhibited mutagenic potential only in the mouse lymphoma assay. In the mouse dominant lethal assay, one study produced positive results while the other resulted in negative data. For all other tests, amitraz was considered negative for genotoxic potential.

C. EXPOSURE

In estimating dietary exposure, amitraz residue values in all commodities except for honey were based on field trials conducted by the registrant. Residue levels in honey were based on the U.S. EPA tolerance. Exposure scenarios considered in this risk assessment included dietary and occupational exposures (both separately and combined). Absorbed dosage estimates were made for acute, seasonal, annual, and lifetime exposures.

For occupational exposure, The absorbed daily dosage (ADD) estimates for amitraz exposure ranged from 0.5 to 46.7 µg/kg/day. For seasonal exposure (60 days for pears, 120 days for cotton, and 365 days for livestock), the average daily dosage (SADD) estimates for amitraz exposure ranged from 0.3 to 22.1 µg/kg/day. The annual average daily dosage (AADD) estimates for amitraz exposure ranged from 0.01 to 3.64 µg/kg/day. The life-time average daily dosage (LADD) estimates for amitraz exposure ranged from 0.005 to 1.94 µg/kg/day. For all of these estimates, the job classification with the highest potential exposure was pear harvesters.

Dietary exposures were also estimated. On the basis of the 95th percentile of user-day exposures for the population subgroups examined, the potential acute dietary exposure of amitraz, from pears, meat, milk, cotton seed, eggs, poultry and honey ranged from 0.4 to 2.3 µg/kg/day. The population sub-group with the largest potential dosage (2.3 µg/kg/day) was "non-nursing infants less than 1 year of age". The potential acute dietary exposure of amitraz, from only pears ranged from 1.4 to 15.3 µg/kg/day. The population sub-group with the largest potential dosage was also "children ages 1 to 6". The exposure estimate for the U.S. population age 16 and older (population sub-group used to estimate acute dietary exposure to agricultural workers) was 5.0 µg/kg/day. The subchronic exposure estimate for the U.S population age 16 and older was 0.2 µg/kg/day (used to estimate seasonal dietary exposure to agricultural workers). The annual average potential chronic dietary exposure to amitraz from pears, meat, milk, cotton seed, eggs, poultry and honey, ranged from 0.09 to 0.7 µg/kg/day. The value for the U.S. population was 0.22 µg/kg/day. The population sub-group with the highest potential exposure was children ages 1 - 6.

Inasmuch as agricultural workers may be exposed to amitraz through work activities or the diet, combined occupational and dietary exposures were determined. The absorbed daily dosage (ADD) estimates for amitraz exposure ranged from 5.5 to 51.7 µ

g/kg/day. For seasonal exposure, the combined seasonal average daily dosage (SADD) estimates for amitraz exposure ranged from 0.2 to 22.3 μg/kg/day. The combined annual average daily dosage (AADD) estimates for amitraz exposure ranged from 0.23 to 3.86 μg/kg/day. The combined life-time average daily dosage (LADD) estimates for amitraz exposure ranged from 0.23 to 2.16 μg/kg/day. The job classification with the highest potential exposure each time period was pear harvesters.

D. RISK CHARACTERIZATION

On the basis of the indicated effects and estimated dosages, margins of safety, defined as the ratio of NOEL to the absorbed dose, were calculated for both occupational and dietary exposures to amitraz.

In general, a margin of safety equal to or greater than 10 is considered adequate for the protection of human health when it is based on NOELs from human studies. When exposure is based on NOELs from non-human mammalian studies, an additional factor of 10 is generally used (i.e., MOS of 100). For amitraz, margins of safety for acute exposure were based on human data. Margins of safety for seasonal, annual, and life-time exposures, however, were based on NOELs from non-human mammalian data (i.e., a dog study for seasonal and a mouse study for annual and life-time exposures).

For occupational exposure, margins of safety for acute exposures to amitraz ranged from 3 to 7 for mixer/loader/applicators in pear orchards (5), pear harvesters (3), mixer/loaders involved with the aerial treatment of cotton (4), pilots (7) and flaggers (4). For all other job classifications evaluated, margins of safety for acute exposure to amitraz were greater than 10. For seasonal exposures, the calculated margin of safety for pear harvesters was 11. For all other job classifications evaluated, margins of safety for seasonal exposure to amitraz were at least 100. For chronic (annual) exposures, the calculated margin of safety for pear harvesters was 63. For all other job classifications evaluated, margins of safety for annual exposure to amitraz were greater than 100. For chronic (life-time) exposures, non-oncogenic margins of safety were all greater than 100.

For dietary exposure, the margin of safety for acute exposure to amitraz was 8 for children ages 1 to 6. For all other population subgroups, margins of safety were greater than 10.

For combined (occupational and dietary) exposure, margins of safety for acute exposures to amitraz were ranged from 2 to 8 for mixer/loader/applicators in pear orchards (4), pear harvesters (2), mixer/loader/applicators involved with the ground treatment of cotton (8) mixer/loaders involved with the aerial treatment of cotton (3), pilots (6) and flaggers (4). For field checkers and workers involved with the treatment of livestock, margins of safety for acute exposure to amitraz were at least 10. For seasonal exposures, the calculated margin of safety for mixer/loader/applicators in pear orchards was 96. For pear harvesters the margin of safety was 11. For all other job classifications evaluated, margins of safety for seasonal exposure to amitraz were greater than 100. For chronic (annual) exposures, the calculated margin of safety for pear harvesters was 60. For all other job classifications evaluated, margins of safety

for annual exposure to amitraz were greater than 100. For chronic (life-time) exposures, non-oncogenic margins of safety were all greater than 100.

Cancer risk estimates for occupational exposure to amitraz through the use on pears or cotton, based on the maximum likelihood estimate (Q_1) of the potency slope, ranged from 1.6×10^{-7} to 6.0×10^{-5}. Cancer risk estimates, based on the upper bound (Q_1*) of the potency slope ranged from 3.0×10^{-7} to 1.1×10^{-4}. The occupation with the highest risk was pear harvesters.

Cancer risk estimates for dietary exposure to the U.S. population, based on Q_1 and the Q_1* were, 6.8×10^{-6} and 1.2×10^{-5}, respectively.

For combined occupational and dietary exposures, the calculated risk for agricultural workers using amitraz ranged from 6.9×10^{-6} to 6.7×10^{-5}, when based on the Q_1 . When based on the Q_1*, the cancer risk estimates ranged from 1.3×10^{-5} to 1.2×10^{-4}. The occupation with the highest risk was pear harvesters.

E. CONCLUSIONS

The toxicology data base for amitraz has indicated potential adverse effects in human and laboratory animal studies. Effects reported after acute exposure to the pesticide have generally been associated with the central nervous system. Studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Chronic exposure to amitraz has been associated with an increased incidence of oncogenicity in mice. The genotoxicity data base indicates that amitraz and 2-4-dimethylaniline (a primary plant metabolite and an intermediate mammalian metabolite of amitraz) have mutagenic potential.

Several occupational activities associated with the agricultural use of amitraz, and one population sub-group potentially exposed to amitraz through the diet, have margins of safety less then the values conventionally considered to be protective of human health. In these cases, mitigation should be considered to reduce potential exposure.

Cancer risk estimates for occupational exposures (including dietary) to amitraz through the use on pears, cotton, or livestock, and non-occupational exposures via consumption of commodities treated with amitraz, were between 1 and 12 in 100,000. For dietary exposure only, cancer risk estimates were between 7 and 12 in 1,000,000.

An additional assessment of acute risk potential based on U.S. EPA tolerances indicates that margins of safety based on current U.S. EPA set tolerance levels are less then the values conventionally considered to be protective of human health.

II. INTRODUCTION

This document characterizes the potential risk associated with dietary and occupational exposures to the pesticide amitraz. This assessment was performed under the provisions of the California Birth Defect Prevention Act (Senate Bill 950), and Assembly Bill 2161 (Bronzan). Senate Bill 950 requires a scientific determination that the use of a registered pesticide will not cause significant adverse health effects. The Bronzan bill requires risk assessments on the dietary exposure to pesticides in both raw agricultural commodities and processed foods. Amitraz has been associated with potential adverse effects in mutagenicity, oncogenicity, and reproductive studies.

A. CHEMICAL IDENTIFICATION

Amitraz is the common name for N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)-imino]-methyl]]-N-methylmethanimidamide. Amitraz is presently marketed in the U.S. by Nor-Am Chemical Company as Mitac® EC (emulsifiable concentrate), Mitac® WP (wettable powder), Taktic®, , and Ovasyn®, and by the Upjohn Company as BAAM® EC and BAAM® 50W. Amitraz has both acaricidal and insecticidal properties. It is used against pear psylla; whiteflies on cotton; tetranychid and eriophyid mites on fruit, citrus, ornamental and other agronomic and horticultural crops; eggs and neonate larvae of cotton bollworm; and tobacco budworm. Amitraz is also effective as an animal ectoparasiticide. The exact mode of action for the toxic effects of amitraz is not known. One proposed mechanism is the uncoupling of oxidative phosphorylation (Corbett et al., 1984). Another proposed mechanism is through the interference with octopamine action. It is known that amitraz stimulates the motor output from insect ganglia.

B. REGULATORY HISTORY

Amitraz was developed by the Boots Company Limited in the United Kingdom. Boots licensed the development rights in the United States to the Upjohn Company, and subsequently was granted federal registration of technical amitraz on June 10, 1975. In the following year, the Upjohn Company submitted data to support registration of the emulsifiable concentrate formulation (20% active ingredient (ai)) for use on pears and apples. The submission included an eighty-week oncogenicity study with mice that demonstrated an increase in the incidence of lymphoreticular tumors. Prior to registration of the formulated product, a Rebuttable Presumption Against Registration (RPAR) was issued by the U.S. Environmental Protection Agency (U.S. EPA) in April 1977. The Upjohn Company and the Boots Company jointly submitted rebuttals in response to the RPAR. After review of the oncogenicity study, a Scientific Advisory Panel (SAP) to the U.S. EPA determined, in January 1979, that a statistically significant increase in mouse lymphoreticular tumors had not been shown. The U.S. EPA Cancer Assessment Group (CAG), however, determined that amitraz should be considered a carcinogen, although the evidence was relatively weak. The RPAR process was completed in October 1979, and amitraz was conditionally registered for use on pears. The conditional registration was reissued for a four year period on January 1980. During that period, a two-year oncogenicity study with mice was performed, and the data were submitted to the U.S. EPA. The CAG found a significant increase in the

incidence of hepatocellular tumors in female mice at the high dose level. Amitraz was classified as a possible human carcinogen CQ (quantifiable C carcinogen)(U.S. EPA, 1993).

C. TECHNICAL AND PRODUCT FORMULATIONS

In California, the Nor-Am Company has registered two formulations of amitraz for agricultural use on pears (Mitac® EC and Mitac® WP) and one formulation (Taktic®) for use on livestock. Mitac® EC is an emulsifiable concentrate that contains 19.8 % amitraz. Mitac® WP is a wettable powder containing 50 % amitraz. Taktic® is an emulsifiable concentrate that contains 12.5 % amitraz. The Nor-Am Company has recently petitioned California for a new Section 3 registration amitraz. The new product, Ovasyn®, containing 19.8 % ai, would be used on cotton.

D. USAGE

In 1991, approximately 6,000 pounds of amitraz were used to treat approximately 4,000 acres of pears in California (DPR, 1993a). Amitraz was also used for structural pest control in 1991; however, total usage was less than 1 pound. In 1992, approximately 9,000 pounds of amitraz were used to treat approximately 6,000 acres of pears in California (DPR, 1994a). Approximately 1 pound was used to treat cattle and less than 1 pound was used for structural pest control.

The Mitac® products are registered to control pear psylla and mites on pears. Taktic® is registered to control ticks, mange mites, and lice on cattle and swine. Ovasyn® is intended for use on cotton for the control of bollworm, tobacco budworm, pink bollworm, whitefly, and mites.

Mitac® EC (emulsifiable concentrate) is applied at the rate of 2 to 4 quarts of product per acre, with a 7 day pre-harvest interval. Mitac® WP is applied at the rate of 1.5 to 3 pounds per acre with a 7 day pre-harvest interval. Labels for both products permit a maximum of 9 pounds of active ingredient to be applied per acre during the growing season.

Taktic® can be applied as a 0.06% dip or spray solution to cattle and swine. A second treatment 10 to 14 days later is recommended. A maintenance regimen of treatment every 2 to 3 months is also recommended by the label.

Ovasyn® (currently under review as a Section 3 registration on cotton in California) may be applied at a rate of 0.5 to 0.94 lb ai, per application, with a maximum seasonal use of 1 lb. ai per acre. Reentry of treated areas is not allowed for 24 hours without protective clothing (proposed label).

E. ILLNESS REPORTS

No worker illnesses due to exposure to amitraz have been reported in California from 1982 to 1991 (CDFA, 1983-87; Edmiston and Richmond, 1988; Mehler et al., 1990; Mehler, 1991; and DPR 1993b and 1994b).

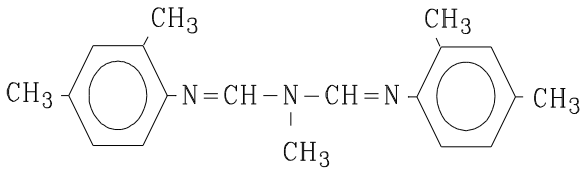
F. PHYSICAL AND CHEMICAL PROPERTIES[1]

1. Chemical Name: N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethyl-phenyl)imino}methyl]]-N-methyl-methanimidamide

2. Common Name: Amitraz

3. Trade Names: Acarac; BAAM® (Upjohn); Mitac®, Ovasyn®, Taktic® (Schering, NOR-AM); Triatox® (Wellcome); Triatix® (Wellcome); Azadieno® (Quimica Estrella); Acadrex® (Shell); Bumetran (Schering); Danicut (Nissan); Edrizar ® (Siapa); Maitac® (Schering); Tudy® (Shell); BTS 27419 (Schering).

4. Structural Formula:



5. Empirical Formula:

$C_{19}H_{23}N_3$

6. CAS Registry Number: 33089-61-1

7. Molecular Weight: 293

8. Physical State: Fine, grayish white powder

9. Melting point 86°C

10. Solubility: 9.3×10^{-5} g/l in water

11. Vapor Pressure: 2.6×10^{-6} mmHg at 25°C

12. Octanol/Water Partition Coefficient: 3.0×10^{5} at pH 5.9

1 Bright, 1987; Bright and Stalker, 1987a; Bright and Stalker, 1987b; Vukich, J.J., 1993; Meister, 1994.

G. ENVIRONMENTAL FATE

The environmental fate studies evaluated in this risk assessment indicate that amitraz is unstable under both light and dark conditions. Hydrolysis appears to be more of a degradation factor than photolysis, and breakdown of the parent compound is pH sensitive. Microbial and chemical degradation is rapid with a half-life of approximately 8 minutes. Other studies have shown that amitraz is rapidly metabolized in plants and does have the potential to leach in various soil types.

1. Hydrolysis/Photolysis

Amitraz is unstable in aqueous solutions under both light and dark conditions. Chemical degradation has been attributed primarily to hydrolysis rather than photolysis (Brehm, 1988; Whiting, 1979). Additionally, the rate of hydrolysis and the resulting degradation products were greatly affected by the pH. In basic solutions (pH 9.2) the primary hydrolysis product was 2,4-dimethylphenyl formamide (BTS 27-919) with smaller amounts of N'-(2,4-dimethylphenyl)-N-methyl formamidine (BTS 27-271). As the pH decreased, the proportion of BTS 27-271 to BTS 27-919 increased and the rate of hydrolysis increased.

2. Microbial Degradation

Amitraz degradation was studied in several sandy-loam and loam soils under aerobic, anaerobic, and sterile conditions (Brehm, 1987). Only small quantities of amitraz and its metabolites were extractable after the first study day. Extractable metabolites from soils exposed to aerobic and anaerobic conditions were primarily composed of BTS 27-271 with smaller quantities of BTS 27-919, and trace amounts of 2,4-dimethylaniline (BTS 24-868) and the parent compound. Under sterile conditions the major degradation products were BTS 27-919 and BTS 27-271. The half-life for amitraz on soil under simulated sunlight was 7.7 minutes. Study results suggested that both chemical (hydrolysis) and microbial degradation occurred.

3. Mobility (soil, air, water, plants)

Data submitted to the federal and California regulatory agencies indicate that leaching of amitraz may occur in some soil types (U.S. EPA, 1987a; Somerville and Nicholson, 1976). Amitraz was found to be moderately mobile in sandy loam, silt loam, and clay soils, and very mobile in sandy soil.

4. Plant Residues/Metabolism

The metabolism of radio-labeled (^{14}C) amitraz has been investigated in pears (McGibbon and Kelly, 1984). Amitraz was applied to pears at an application rate of 0.06% ai at two test sites. At harvest (either 29 or 61 days after treatment), approximately 48% of the applied radioactivity remained in the fruit (45% in the 29 day samples and 52% in the 61 day samples). The distribution of the recovered radioactivity between the organic soluble, aqueous soluble and fiber bound fractions was 34.8, 22.3, and 42.9% respectively for the 29 day samples. For the 61 day samples the fractions were 33.7, 30.9, and 35.5% for the organic soluble, aqueous soluble and fiber bound fractions, respectively. In the 29 day samples, the primary metabolites were BTS 27-271 (N-(2,4-dimethylphenyl)-N'-methyl-formamidine) and BTS 27-919 (2,4-dimethylformanilide), accounting for 16.4 and 4.7%, respectively for the recovered radioactivity. BTS 24-868 (2,4-dimethylaniline), BTS 28-037 (N,N'-bis-2,4-dimethylphenyl formamidine), and amitraz were present in smaller quantities, accounting for 1.3, 1.2, and 0.5%, respectively of the recovered radioactivity. In the 61 day samples, the primary metabolites were also BTS 27-271 and BTS 27-919, accounting for 11.6 and 5.9%, respectively for the recovered radioactivity. BTS 24-868, BTS 28-037, and amitraz were present in smaller quantities, accounting for 1.1, 1.1, and 1.3%, respectively of the recovered radioactivity. One metabolite, 2,4-dimethylaniline (BTS 24-868) has been associated with pulmonary tumors in female HAM/ICR mice (Weisburger, et al, 1978) discussed by Thomas (1984). Furthermore, 2,4-dimethylaniline was found to express genotoxic potential in the L5178Y mouse lymphoma gene mutation assay (McGregor and Riach, 1983a)). Other potential plant metabolites may include compounds, such as dimethylamine, that have been shown to cause liver tumors in mice (U.S. EPA, 1987b; and Thomas, 1984)

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS/METABOLISM

The urinary excretion of amitraz-derived radioactivity by rats, mice, baboon, and humans following a single oral dose was reported by Campbell (1984). With the exception of the humans, who were dosed at 0.25 mg/kg, all species were dosed at 10 mg/kg. In all four species, urine was the major route of excretion, accounting for 65-83% of the dose. No significant differences were evident between species or sexes, in terms of percentage excreted in the urine. In all species, 55-74% of the dose was excreted in the urine within the first 24 hours after dosing. In humans, approximately 82% of the administered dose of amitraz was excreted in the urine within 72 hours of dosing. Using thin layer chromatography, the spectrum of metabolites observed was similar in all species investigated. In the rat, the two largest fractions were a band containing BTS 39-098 (4-formamido-3-methyl benzoic acid) and FBC 31-158 (4-acetamido-3-methyl benzoic acid), and a second band containing BTS 39-098, FBC 31-158, and BTS 28-369 (4-amino-3-methylbenzoic acid). The first band (Band A) accounted for approximately 26% of the total urinary radioactivity. The second band (Band B) accounted for approximately 54% of the total. In humans, similar results were observed. Within the first 24 hours, greater than 50% of the dose was excreted. By 48 hours, 75% of the dose was excreted. Using thin layer and gas chromatography, the spectrum of metabolites identified was similar to that previously observed in rats, mice, and baboons. The major metabolites in human urine were FBC 31-158 and BTS 39-098. These metabolites accounted for 27.1% of the radioactivity excreted. A polar material, consisting of conjugates of FBC 31-158, BTS 39-098 and BTS 28-369, accounted for 59.6%. In baboons, the pattern was essentially identical to that observed in the rats and humans. In the mouse, the pattern was consistent, however, the percentages were slightly different. Band A accounted for approximately 16% of the total urinary radioactivity while Band B accounted for approximately 62% In all species examined, BTS 27- 271 (N-(2,4-dimethylphenyl)-N'-methyl-formamidine) accounted for 3.1 to 6.5 % of the total urinary excretion. BTS 24-868 (2,4-dimethylaniline) was found in very small quantities (< 1%) and was assumed to be an intermediate metabolite in mammals.

In conclusion, following a single oral dose, amitraz is rapidly metabolized and excreted primarily in the urine. The rates and routes of excretion are similar in humans, baboons, rats, and mice. Furthermore, the spectrum of metabolites observed was similar in all species investigated. Based on the urinary excretion data reported in humans, oral absorption of amitraz was assumed to be at least 82%

B. ACUTE TOXICITY

SUMMARY

Clinical signs associated with acute exposure of laboratory animals to amitraz included: central nervous system depression, ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. Clinical signs or symptoms

reported in humans treated with amitraz included: paleness, dry mouth, drowsiness, slurred speech, disorientation, and loss of consciousness. These effects were observed following a single oral dose of 0.25 mg/kg. An acute NOEL of 0.125 mg/kg was established from human data.

1. Animal Studies

The acute toxicity profile for technical grade amitraz (97 to 99% active ingredient) is summarized in TABLE I. As indicated in the table, the LD_{50}'s (the dose required to cause death in 50% of the exposed population) ranged from 100 to greater than 1,600 mg/kg. On the basis of lethality after oral exposure, the most sensitive animals were dogs and baboons. These animals were at least 4 times more sensitive than rats, mice, and guinea pigs.

TABLE I: Amitraz: Acute toxicity of technical grade material

Amitraz (technical)	
Oral LD_{50} (rat)	515-593 mg/kg (Shaw, 1973a)
Oral LD_{50} (mouse)	>1,600 mg/kg (Patton & Sutton, 1971)
Oral LD_{50} (guinea pig)	400-800 mg/kg (Patton & Sutton, 1971)
Oral LD_{50} (rabbit)	>100 mg/kg (Patton & Sutton, 1971)
Oral LD_{50} (dog)	100 mg/kg (Patton & Sutton, 1971)
Oral LD_{50} (baboon)	100-250 mg/kg (Patton, 1973)
Dermal LD_{50} (rat)	>1,600 mg/kg (Patton & Sutton, 1971)
Inhalation LC_{50} (rat, 6-hour)	2.4 mg/L (Berczy, et al., 1972)
Dermal Sensitization (guinea pig)	negative (Sutton, 1971)
Dermal Irritation (rabbit)	negative (Metcalf, 1972)
Eye Irritation (rabbit)	negative (Sutton, et al., 1972)

The acute toxicity profile for various amitraz containing formulations is summarized in TABLE II. Of interest is the fact that the oral LD_{50} for rats is lower for the 20% active ingredient formulation than for the technical grade material. This suggests that an inert ingredient(s) (defined as something other than the ai) in the product formulation increases the acute oral toxicity in the rat. A comparison between TABLEs I and II also reveals that increased dermal irritation is reported in the formulations.

TABLE II: Amitraz: Acute toxicity of formulation products

Amitraz (20% emulsifiable concentrate - Mitac® /BAAM® EC)	
Oral LD_{50} (rat)	200-400 mg/kg (Shaw & Williams, 1975)
Dermal LD_{50} (rabbit)	>1,000 mg/kg (Weddon & Gargano, 1975a)
Inhalation LC_{50} (rat)	>2.3 mg/L (Weddon & Gargano, 1975b)
Dermal Irritation (rabbit)	moderate (Weddon & Gargano, 1975a)
Dermal Irritation (guinea pig)	negative (Weddon & Gargano, 1975b)
Dermal Irritation (human)	moderate (Hall, 1973)
Skin Sensitization (guinea pig)	negative (Weddon & Gargano, 1975b)
Eye irritation (rabbit)	moderate-severe (Weddon & Gargano, 1975b)
Amitraz (12.5% emulsifiable concentrate - Taktic® EC)	
Oral LD_{50} (rat)	2,000 mg/kg (Sharp & Saunders, 1984)
Dermal LD_{50} (rat)	>2,043 mg/kg (Sharp & Saunders, 1983)
Dermal Irritation (rabbit)	moderate (Liggett, 1983a)
Eye irritation (rabbit)	mild (Liggett, 1983a)
Amitraz (50% wettable powder - Mitac® /BAAM® 50W)	
Oral LD_{50} (rat)	1,427 mg/kg (Seaman & Brown, 1979a)
Dermal LD_{50} (rabbit)	>2,000 mg/kg (Seaman & Brown, 1979b)
Dermal Irritation (rabbit)	mild (Seaman & Brown, 1979b)
Eye irritation (rabbit)	moderate (Seaman & Brown, 1979c)
Inhalation LC_{50} (rat, 4 hr)	>1.6 mg/L (Kakuk, 1979a)

2. Human Studies

The acute toxicologic effects of amitraz in humans have been reported in a urinary excretion study by Campbell and Needham (1984)(also see pharmacokinetics). A single oral dose (0.25 mg/kg) of ^{14}C-amitraz was given to two male human volunteers. Approximately 90 minutes after dosing, one subject was pale and complained of a dry mouth, drowsiness, and disorientation. Ten minutes later the subject lost consciousness. The subject was "rousable" but was not fully conscious for 6 hours. Approximately 160 minutes after dosing, the second subject complained of a dry mouth, and a light headed feeling. He also exhibited slurred speech.

In a more recent study, the effects of amitraz on human subjects were investigated (Cass 1992). Six adult males were administered oral doses of amitraz in a double blind crossover study. At the completion of the study, each of the six volunteers had been treated three times (0.0625 mg/kg, 0.125 mg/kg and a placebo control). The treatments were administered, with 150 ml water,

30 minutes after the subjects had eaten breakfast. No clinically significant changes in vital signs or ECG parameters were reported. Hematology, blood chemistry and urine parameters were reported to be unaffected by treatment. Pupil responsiveness and psychomotor performance were also reported to be unaffected by amitraz treatment. The NOEL established by this study was 0.125 mg/kg.

The acute NOEL used for this risk assessment was obtained from the two human metabolism studies (see Hazard ID Section for additional discussion of the studies). On the basis of the observed clinical signs (i.e., paleness, dry mouth, drowsiness, slurred speech, disorientation, and loss of consciousness), the NOEL for acute exposure to amitraz was assumed to be **0.125 mg/kg** (highest non effective dose tested).

C. SUB-CHRONIC TOXICITY

SUMMARY

The following sub-chronic toxicity tests were performed with amitraz: a dermal toxicity study in rabbits; oral toxicity studies in rats, mice and dogs; and dietary studies in rats and mice. At high doses (e.g., 200 mg/kg/day), effects included, dermal erythema, dermal desquamation, subcutaneous hemorrhage, diarrhea, lethargy, emaciation, weight loss, squealing, and death. At low doses (e.g., at or near 3 mg/kg/day) the most prevalent clinical effect was a decrease in body weight gain. On the basis of CNS depression and catarrhal conjuctivitis reported in an oral study in dogs, a NOEL of 0.25 mg/kg/day was established for sub-chronic exposure to amitraz. NOELs established in each of the reported studies are presented in TABLE III:

TABLE III: Amitraz: Sub-Chronic Toxicity

Study	NOEL	Effects
3-week Dermal Toxicity (Rabbits)	<3.3 mg/kg/day	sedation, dermal erythema and desquamation, subcutaneous hemorrhage, diarrhea, loss of body weight and increased blood sugar.
90-day Oral Toxicity (Rats)	3 mg/kg/day	decreased body weight gain.
4-week Oral Toxicity (Mice)	<3 mg/kg/day	decreased body weight gain.
90-day Oral Toxicity (Dogs)	0.25 mg/kg/day	CNS depression and catarrhal conjuctivitis.
3-month Dietary Toxicity (Rats)	3 mg/kg/day	decreased body weight gain, increase in brain weight as a function of body weight.
3-month Dietary Toxicity (Mice)	<3 mg/kg/day	decreased body weight gain.

1. Dermal Toxicity Study (Rabbits)

The dermal toxicity of amitraz was evaluated by applying the compound (in acetone) to the backs (10cm^2) of New Zealand white rabbits at applied dosages of 0, 50, or 200 mg/kg/day (approximately 0, 12, or 44 mg/cm^2) (Sutton 1993a). Assuming a dermal absorption of 13.8% (Haskell, 1994), the adjusted absorbed dosages were 0, 6.9, or 27.6 mg/kg/day. Each dose group consisted of four males and four females. Exposures were for 3 weeks, 5 days per week. Clinical signs observed after both 50 and 200 mg/kg/day included sedation, dermal erythema, dermal desquamation, subcutaneous hemorrhage, diarrhea, an increase in blood glucose, and a decrease in body weight gain (control animals gained an average of 0.17 mg/kg, animals in the 50 mg/kg/day group lost an average of 0.13 mg/kg, and animals in the 200 mg/kg group lost 0.93 mg/kg). Tubular degeneration in the testes of all four males in the 200 mg/kg/day was reported. No treatment-related gross pathology was reported. The NOEL for this study was < 50 mg/kg/day based on the potential adverse effects reported. While this study clearly demonstrates chemical related effects, interpretation of these results was hindered by a number of deficiencies. The deficiencies included: a lack of test article analysis; the test article stability and chemical lot numbers were not reported; only 4 animals per sex per dose were used; only 2 dose levels were used; and the study failed to establish a NOEL. This study was not acceptable (and not upgradable) to the DPR as a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guideline study.

2. Oral Study (Rat)

A 90-day toxicity study was conducted in Ash-Wistar rats (Sutton and Williams, 1971). The test article was administered by oral intubation, at 0, 3, 12, 50, or 200 mg/kg/day. Each treatment group consisted of 21 males and 21 females. The control group consisted of 42 males and 42 females. While all treatment groups were to be exposed for 90 days, the exposure regimen for the 200 mg/kg/day and the 50 mg/kg/day groups was modified due to adverse clinical signs. The animals in the 200 mg/kg/day group were reported to have become irritable after treatment. Subsequent signs included hunched backs, lethargy, weakness, and emaciation. The animals lost weight and squealed when handled. Due to the severity of these signs, this group of animals was killed after 7 days of treatment. Microscopic examination revealed; congestion of major organs, principally the heart, liver, kidneys and spleen, and less often, the adrenals and pituitary. Additional lesions included early signs of thymic involution and an increased incidence of periportal vacuolation in the liver. Animals in the 50 mg/kg/day group exhibited abnormal behavior (i.e., excitability, aggressiveness and continual squealing) after two days of dosing. Due to the progressive nature of this behavior, the animals were removed from treatment after 7 days. They were retained for 11 weeks without treatment then treated for an additional 7 days then euthanized. Microscopic lesions observed in these rats included congestion of the spleen in both sexes and congestion of the kidneys in females. Females were reported to show early signs of thymic involution and loss of acinar structure. Males were reported to have emphysematous lungs and swollen acini of the salivary gland. Animals in the 12 and 3 mg/kg/day groups were maintained on treatment for the entire 90 days. Animals in the 12 mg/kg/day group exhibited a slight decrease (8%) in total weight gain when compared to control animals. No histological changes were attributed to treatment in this group. No effects on weight gain were detected in the animals from the 3 mg/kg/day group. On the basis of the decreased body weight gain, the NOEL established for this study was 3 mg/kg/day. This study contained a number of deficiencies, however, that hindered interpretation. These deficiencies included; a lack of chemical analysis, stability and identification; and the absence of eye examinations. This study was not acceptable (and not upgradable) to DPR as a FIFRA guideline study.

3. Oral Study (Mouse)

A 90-day toxicity study was conducted with four week old CFLP mice (Shaw and Williams, 1971). The test article was administered by oral intubation, at 0, 3, 12, 50, or 200 mg/kg/day. Each dose group consisted of 10 males and 10 females. At 200 mg/kg/day, 8 out of 20 animals died during the first 3 weeks of treatment. Deaths in the other groups were 2/20, 1/20, 0/20, and 2/20 for the 50, 12, 3 mg/kg/day, and control groups, respectively. A significant ($p<0.05$) decrease in body weight gain was detected in all treated groups when compared to concurrent controls (weight gain was 9.4, 8.3, 7.5, 5.7, and 2.1 grams for

animals from the 0, 5, 12, 50, and 200 mg/kg/day dose groups, respectively). The percentage of total body weight that these values represent are 30.1%, 26.2%, 23.7%, 17.6%, and 6.5%, for animals from the 0, 5, 12, 50, and 200 mg/kg/day dose groups, respectively. With respect to organ weight (represented as a percentage of body weight), a significant ($p<0.05$) increase was observed at 50 and 200 mg/kg/day for liver, kidney, and spleen. At 12 mg/kg/day, a significant ($p<0.05$) increase was observed for the kidney. Histologic examinations revealed slight to moderate hepatocyte and nuclear enlargement in the 200 mg/kg/day group. Slight hepatocyte and/or nuclear enlargement was observed in 3 males given 50 mg/kg/day and one male given 12 mg/kg/day. On the basis of the observed decrease in body weight gain, the NOEL established for this study was <3 mg/kg/day.

4. Oral Study (Dog)

A 90-day toxicity study was conducted with dogs (Patton and Williams, 1973). The test article was administered in gelatin capsules at doses of 0, 0.25, 1, or 4 mg/kg/day. Four animals (2 males and 2 females) were treated in each dose group. All animals given 4 mg/kg/day exhibited signs of central nervous system depression 3 hours after dosing. Other signs of acute toxicity included vomiting, ataxia, subnormal rectal temperature, and subnormal pulse rate (specific temperatures and pulse rates were not reported). Animals in the treated groups exhibited an increase in relative liver weight (when compared to control, increases were 10%, 14%, and 28% for low, mid, and high doses respectively). Varying degrees of acute catarrhal conjuctivitis was observed in dogs 8 weeks after administration of 4 mg/kg/day. To a lesser degree, conjuctivitis was also reported in animals receiving 1 or 0.25 mg/kg/day. Histopathology revealed enlargement of the central and midzonal hepatocytes in all dose groups. Hyperplasia of the small periportal hepatocytes and an increase in binucleated cells was also reported. No abnormalities of the central nervous system were attributed to treatment. A DPR review of the study concluded that the effects reported in the liver and the conjuctivitis observed at 0.25 mg/kg/day were not considered to be of toxicological significance. On the basis of the study report and the DPR review, the NOEL for this study was assumed to be 0.25 mg/kg/day. This study had a number of deficiencies that rendered it unacceptable as a FIFRA guideline study. These deficiencies include inadequate number of animals per group, no analysis of dosing material, no purity stated, inadequate pathology report, no individual clinical signs and no severity grades.

5. Dietary Study (Rat)

Male and female Wistar rats were exposed to amitraz (10 animals per sex per dose group) in their feed for three months (Toyoshima and Fujita, 1972a). Dosage groups included 0, 3, 12, and 50 mg/kg/day. A significant ($p<.05$) decrease in body weight gain was reported in the 12 and 50 mg/kg groups. A significant increase ($p<.05$) in relative organ weights was also detected. At 50 mg/kg/day, relative organ weight increases were seen in the brain, heart, lungs, liver, kidneys, spleen, seminal glands, and thymus glands. At 12 mg/kg/day, a significant ($p<0.05$) increase in relative organ weight was present only in the brain. On the basis of the above findings, the NOEL established for this study was 3 mg/kg/day.

6. Dietary Study (Mouse)

Male and female ICR SLC mice were exposed to amitraz in their feed for three months (Toyoshima and Fujita, 1972b). Dosage groups included 0, 3, 12, and 50 mg/kg/day. Each dosage group consisted of 13 males and 13 females. A significant ($p<.05$) decrease in body weight gain was reported for all three dose groups (note: while the response was reported to be statistically significant, individual data were not reported). Organ weight effects attributed to treatment were also investigated. When organ weights were expressed in relation to body weight, a significant increase ($p<0.05$) in brain (14%) and heart (23%) weight was observed at 50 mg/kg/day. In that dose group, a significant ($p<0.05$) decrease in relative kidney weight (9%) was detected only in females. At 12 mg/kg/day, a significant ($p<0.05$) decrease in relative heart weight (20%) was reported for both sexes. The NOEL for this study was <3 mg/kg/day, based on suppression of body weight gain.

D. CHRONIC TOXICITY AND ONCOGENICITY

SUMMARY

The chronic toxicity and/or oncogenic potential associated with chronic exposure to amitraz was evaluated in dietary studies with rats and mice, and an oral study with dogs. Reported toxic effects included central nervous system depression, depressed growth rate, and reduction in food intake. On the basis of the time of onset, the central nervous system effects were considered acute. For chronic toxicity, a LOEL of 2.3 mg/kg/day was established based on liver hyperplastic nodules in females, and hyperkeratosis of the forestomach of male mice. An estimated NOEL of **0.23 mg/kg/day** was calculated using a default procedure of dividing the LOEL of 2.3 mg/kg/day by an uncertainty factor of 10 (U.S. EPA, 1987c). No significant induction of tumors was reported in rats. In CFLP mice, an increase in lymphoreticular and lung tumors were detected in females, while liver tumors were detected in both males and females. Only the lymphoreticular tumors, however, were significant at the 0.05 level. In B6C3F1 mice, a significant increase in liver tumors was detected in females, while a

significant increase in lung tumors was detected in males. See TABLE IV for a summary of the chronic toxicity and oncogenicity of amitraz.

TABLE IV: Amitraz: Chronic Toxicity and Oncogenicity.

Species	Chronic Toxicity NOEL	Oncogenicity
Beagles	0.25 mg/kg/day (Acute)[a] 1.0 mg/kg/day (Chronic)[b] (0.25 mg/kg/day U.S. EPA)	None reported
CFLP mice	2.8 mg/kg/day (Chronic)[c]	Significant increase in lymphoreticular tumors in females Slight increase in liver tumors in both sexes. Slight increase in lung tumors in females.
B6C3F1 mice	0.23 mg/kg/day (Chronic)[d,e]	Increased hepatocellular carcinomas and adenomas in females (increased hyperplastic nodules also reported). Increased lung tumors and liver hyperplastic nodules in males.
Wistar rats	2.5 mg/kg/day (Chronic)[f]	None reported.

a NOEL based on CNS depression.
b NOEL based on a lack of chronic toxicity at highest dose tested.
c NOEL based on decreased body weight gain.
d LOEL based on liver hyperplastic nodules in females, and hyperkeratosis of the forestomach in males.
e Adjusted NOEL calculated by dividing the LOEL by an uncertainty factor of 10.
f NOEL based on decreased body weight gain.

1. Oral Toxicity Study (Dog)

Groups of beagles (4 male and 4 female) were exposed to amitraz in a two-year oral toxicity study (Morgan et al., 1983). The compound was administered in gelatin capsules, at 0, 0.1, 0.25, or 1.0 mg/kg/day. All animals in the high dose group (1.0 mg/kg/day) exhibited slight CNS depression 3 hours after dosing on days 1 and 2. The study report failed, however, to report the specific CNS signs observed. Subsequently, all dogs appeared clinically normal. No effects were reported for food consumption or body weight gain. Furthermore, routine hematology, blood biochemistry, and urinalysis were considered to be within normal limits. Since effects reported in this study were acute rather than chronic in nature, the chronic NOEL for this study is assumed to be greater than or equal to 1.0 mg/kg/day, the highest dose tested. Due to report deficiencies (no description of test article, no age at start, and no MTD), DPR initially considered the study unacceptable as a FIFRA guideline study. After submission of additional information, the study was considered acceptable. The U.S. Environmental Protection Agency considered the NOEL for this study to be 0.25 mg/kg/day (U.S. EPA, 1993). With an uncertainty factor of 100, the U.S. EPA set the Reference Dose (RfD) at 0.0025 mg/kg/day.

2. Dietary Study (CFLP Mouse)

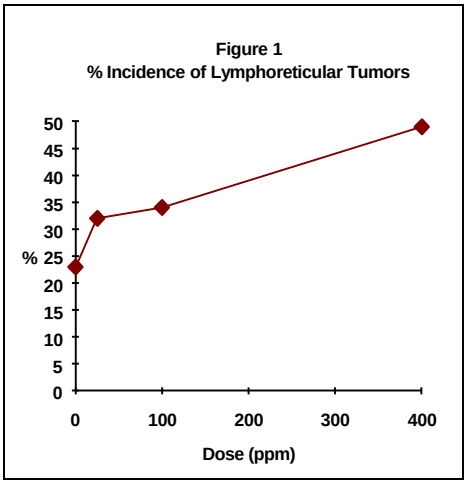
A test was performed to assess the carcinogenic potential of amitraz in CFLP mice (Burnett, et al., 1976). Animals were exposed to amitraz, in their diet, at 0, 25, 100, or 400 ppm (0, 2.8, 12.5, or 66.5 mg/kg/day for males; and 0, 4.1, 16.3, or 84.4 mg/kg/day for females). Treatment was for 80 weeks and each exposure group consisted of 50 males and 50 females. No signs of acute toxicity were noted during the initial days of exposure. Throughout the study, a reduction in weight gain ($p<0.05$), when compared to controls, was reported in all treated groups for both sexes. On the basis of overall body weight, however, only the reduction observed at 400 ppm (i.e., 38% and 18% reduction for males and females, respectively) was considered biologically significant.

TABLE V: Incidence of Lymphoreticular Tumors in Female CFLP Mice Fed Amitraz for 80 Weeks (Burnett et al., 1976).

Lymphoreticular Tumors				
Observation	**Dose (ppm)**			
	0	25	100	400
Animals Examined	(43)	(44)	(44)	(47)
Lymphoreticular Tumors[a]	10++	14	15	23**
Tumor Percentage	23%	32%	34%	49%

a Historical Range = 2 - 38%
++ Trend test significant at p<0.01 by the Cochran-Armitage linear trend test.
** Statistically Significant from the control group at p<0.01 by the Fischer's Exact Test.

Oncogenic effects were reported in both females and males. Females exhibited a dose-related increase (10/43, 14/44, 15/44, and 23/47) in lymphoreticular tumors (TABLE V and Figure 1). The increase over controls was significant (p<0.01) at 400 ppm (84.4 mg/kg/day). The slides from this study have been reviewed by a number of pathologists (Kakuk, 1978). While all pathologists reported an increase in lymphoreticular tumors, the incidence (and therefore the statistical significance) varied from pathologist to pathologist.



Using Fisher exact comparisons, p values ranged from 0.0002 to 0.178. Due to the extreme variability of the reviews, the original data were used by DPR.

Other indicators of oncogenic potential included increases in pulmonary adenomas in females (TABLE VI; and Figure 2) and in hepatocellular tumors in males and females (TABLES VII and VIII; and Figures 3-4). When compared to control values, none of the values were statistically significant at $p \leq 0.05$. A linear trend test (Cochran-Armitage) did, however, indicate statistical significance ($p < 0.05$) for hepatocellular adenomas and combined adenomas and carcinomas in CFLP female mice (TABLE VII). Due to report deficiencies

(i.e., no test article description, limited histopathology, no diet analysis, animal husbandry problems), DPR considered the study unacceptable as a FIFRA guideline study. The data did, however, add to the weight of evidence that amitraz has oncogenic potential.

TABLE VI: Incidence of Pulmonary Adenomas in Female CFLP Mice Fed Amitraz for 80 Weeks (Burnett et al., 1976).

Pulmonary Adenomas				
Observation	**Dose (ppm)**			
	0	25	100	400
Animals Examined	43	44	44	47
Pulmonary Adenomas[a]	10	14	9	16
Tumor Percentage	21%	32%	21%	34%

a Historical Range = 2 - 28%

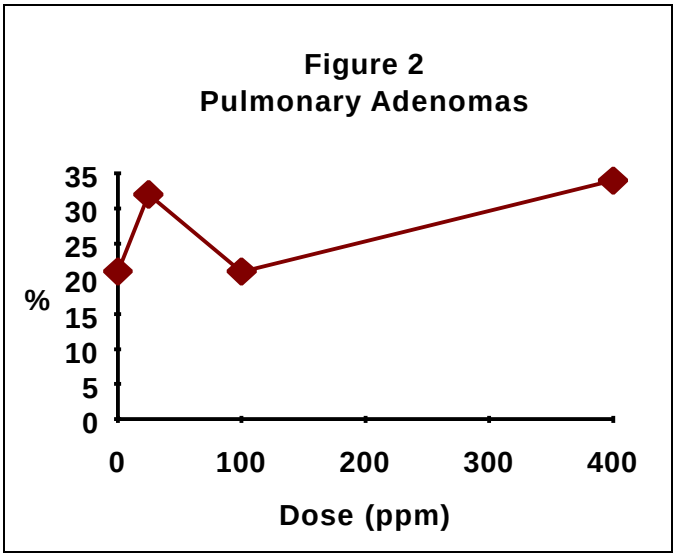


TABLE VII: Incidence of Liver Tumors in Female CFLP Mice Fed Amitraz for 80 Weeks (Burnett et al., 1976).

Liver Tumors				
Observation	**Dose (ppm)**			
	0	25	100	400
Animals Examined	43	44	44	47
Hepatocellular Adenomas[a]	0+	0	0	3
Tumor Percentage	0%	0%	0%	6%
Hepatocellular Carcinomas[b]	0	0	2	0
Tumor Percentage	0%	0%	5%	0%
Adenomas/Carcinomas[c]	0+	0	2	3
Tumor Percentage	0%	0%	5%	6%

a Adenoma historical range = 2 - 16%
b Carcinoma historical range = 0 - 8%
c Adenoma/Carcinoma historical range = 2 - 24%
+ Trend significant at $p<0.05$ by the Cochran-Armitage linear trend test

Figure 3
Adenomas

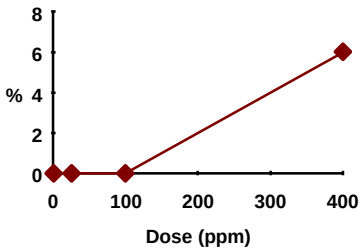


Figure 4
Carcinomas

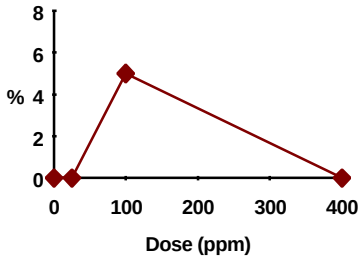


Figure 5
Adenomas & Carcinomas

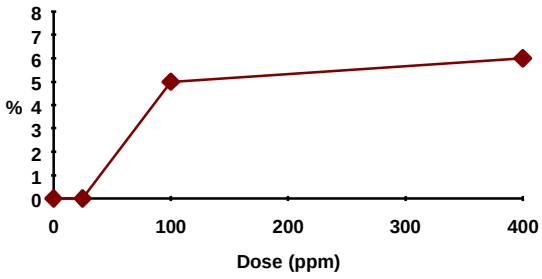


TABLE VIII: Incidence of Liver Tumors in Male CFLP Mice Fed Amitraz for 80 Weeks (Burnett et al., 1976).

Liver Tumors				
Observation	**Dose (ppm)**			
	0	25	100	400
Animals Examined	43	47	46	46
Hepatocellular Adenomas[a]	5	8	5	9
Tumor Percentage	12%	17%	11%	20%
Hepatocellular Carcinomas[b]	1	3	4	3
Tumor Percentage	2%	6%	9%	7%
Adenomas/Carcinomas[c]	6	11	9	12
Tumor Percentage	14%	23%	20%	26%

a Adenoma historical range = 2 - 38%
b Carcinoma historical range = 0 - 4%
c Adenoma/Carcinoma historical range = 2 - 38%

Figure 6
Adenomas

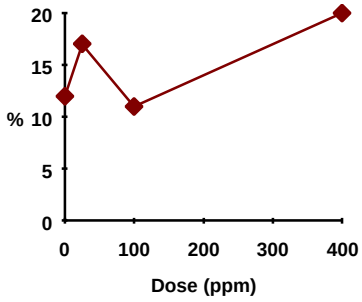


Figure 7
Carcinomas

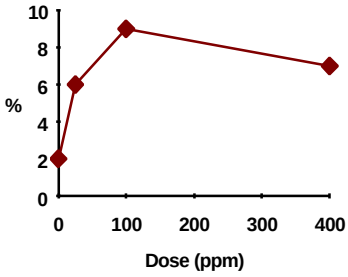
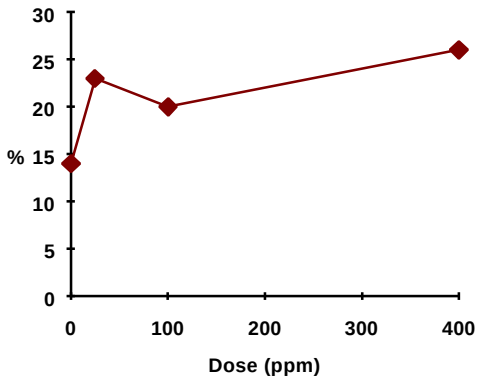


Figure 8
Adenomas & Carcinomas



3. Dietary Study (B6C3F1 Mouse)

Male and female B6C3F1 mice (75/sex/treatment group, 100/sex in controls) were administered amitraz (for 104 weeks) in their diet at 0, 25, 100, or 400 ppm (0, 2.3, 9.6, or 44.7 mg/kg/day for males; and 0, 2.6, 10.8, or 50.1 mg/kg/day for females)(Colley, et, al., 1983). Decreased body weight gain and food consumption were present at 100 and 400 ppm for both sexes. A dose related increase in the number of males with hyperkeratosis of the forestomach was reported (TABLE IX; and Figure 9). All increases in the males were statistically significant ($p<0.001$). Increases in females were statistically significant ($p<0.05$) at 25 and 100 ppm (TABLE IX; and Figure 10. Figure 11 illustrates the response when male and female responses are combined.

TABLE IX: Incidence of Forestomach Hyperkeratosis in Male and Female B6C3F1 Mice Fed Amitraz for 104 Weeks (Colley et al., 1983).

Forestomach Hyperkeratosis				
Observation	**Dose (ppm)**			
	0	25	100	400
Animals Examined	100	75	75	75
Male				
Hyperkeratosis	22^{+++}	37***	39***	52***
Percentage	22%	49%	52%	69%
Female				
Hyperkeratosis	27	32*	35*	20
Percentage	27%	43%	47%	27%

a Historical Range = 5 - 18%
* Significantly different from control group at $p<0.05$ by the Fisher's Exact Test.
*** Significantly different from control group at $p<0.001$ by the Fisher's Exact Test.
+++ Cochran-Armitige trend test $p<0.001$

Figure 9
Male

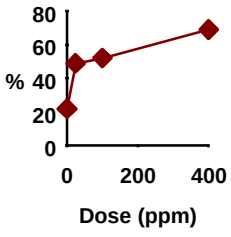


Figure 10
Female

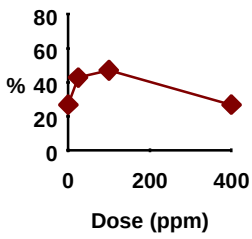
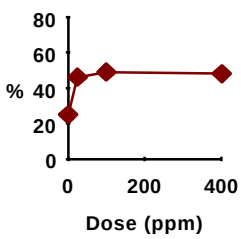


Figure 11
Male and Female



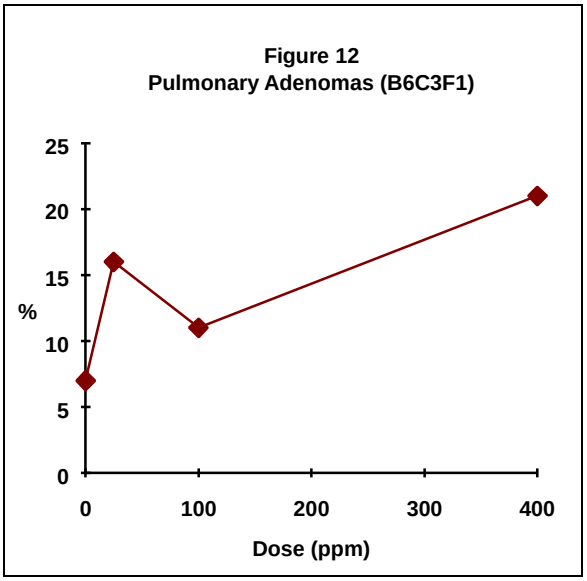
Males also exhibited increases in the number of animals with lung adenomas (pulmonary adenomas)(TABLE X). The number of animals affected were statistically significant ($p<0.01$) at 400 ppm.

TABLE X: Incidence of Pulmonary Adenomas in Male B6C3F1 Mice Fed Amitraz for 104 Weeks (Colley et al., 1983).

Pulmonary Adenomas

Observation	Dose (ppm)			
	0	25	100	400
Animals Examined	100	75	75	75
Pulmonary Adenomas[a]	7+++	12	8	16**
Tumor Percentage	7%	16%	11%	21%

a Historical Range = 5 - 18%
** Significantly different from control group at $p<0.01$ by the Fisher's Exact Test.
+++ Cochran-Armitige trend test $p<0.01$



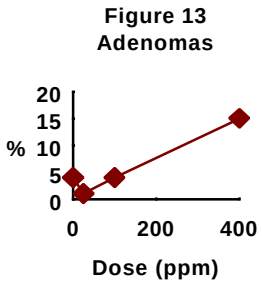
In the liver, dose related increases in the number of females exhibiting hyperplastic nodules, adenomas, and carcinomas was reported (TABLE XI). A positive trend ($p<0.001$, Cochran-Armitige trend test) was reported for each. Statistically significant increases in hepatocellular carcinomas ($p<0.001$), hepatocellular adenomas ($p<0.01$), and hyperplastic nodules ($p<0.001$) were reported for the 400 ppm group. When adenomas and carcinomas were

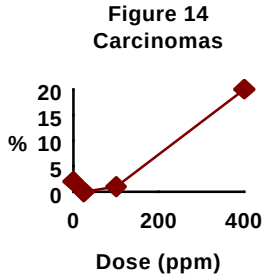
combined, a positive trend (p<0.001, Cochran-Armitige trend test) with a statistically significant increase (p<0.001) at 400 ppm was reported.

TABLE XI: Incidence of Liver Tumors and Hyperplastic Nodules in Female B6C3F1 Mice Fed Amitraz for 104 Weeks (Colley et al., 1983).

Liver Tumors and Hyperplastic Nodules				
Observation	**Dose (ppm)**			
	0	25	100	400
Animals Examined	100	75	75	75
Hepatocellular Adenomas[a]	4+++	1	3	11**
Percentage	4%	1%	4%	15%
Hepatocellular Carcinomas[b]	2+++	0	1	15***
Percentage	2%	0%	1%	20%
Adenomas/Carcinomas[c]	6+++	1	4	26***
Percentage	6%	1%	5%	35%
Hyperplastic Nodules	3+++	7	11	46***
Percentage	3%	9%	15%	61%

a Adenoma Historical Range = 4 - 14%
b Carcinoma Historical Range = 4 - 6%
c Adenoma/Carcinoma Historical Range = 8 - 20%
** Significantly different from control group at p<0.01 by the Fisher's Exact Test.
*** Significantly different from control group at p<0.001 by the Fisher's Exact Test.
+++ Cochran-Armitige trend test p<0.001





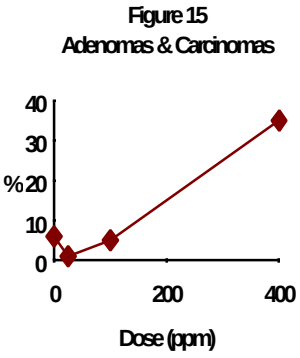
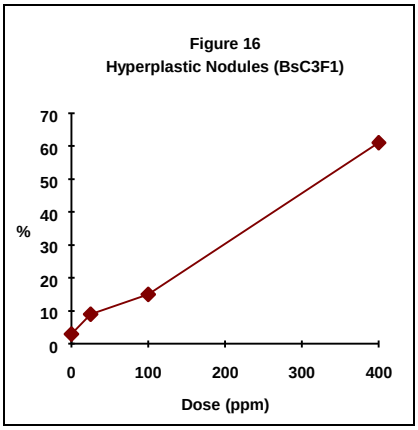


Figure 16 is a graphic representation of the hyperplastic nodules reported in female B6C3F1 mice (Colley et al., 1983; see TABLE XI). The figure illistrates the dose-related increase in hyperplastic nodules from 0 to 400 ppm. the response at 400 ppm was statistically significant ($p<0.001$) using Fisher's Exact Test.



On the basis of the increase in liver hyperplastic nodules and forestomach hyperkeratosis (TABLE IX), the LOEL for this study was 25 ppm (2.3 mg/kg/day). An estimated NOEL of **0.23 mg/kg/day** was calculated using a default procedure of dividing the LOEL of 2.3 mg/kg/day by an uncertainty factor of 10 (U.S. EPA, 1987c). DPR considered the study acceptable as a FIFRA guideline study.

4. Combined Toxicity/Oncogenicity Study (Rat)

Amitraz was administered in the diet to Wistar rats (40/sex/group) at 0, 15, 50, or 200 ppm (0, 0.77, 2.50, or 10.18 mg/kg/day for males; and 0, 0.97, 3.13, or 12.59 mg/kg/day for females)(Sutton and Offer, 1973). The NOEL for this study was 50 ppm (3.13 mg/kg/day for females) based on reduced body weight gain (13%) in females in the high dose group. No significant changes in the incidence of tumors between treated and control animals were detected. Due to a number of deficiencies, however, DPR initially considered this study to be unacceptable as a FIFRA guideline study. The deficiencies included: no analysis of dosing material, no ophthalmology exams, incomplete serum chemistry, an inadequate characterization of the test article, and the lack of a definitive MTD. After submission of rebuttal and additional data, the study was upgraded to acceptable.

E. GENOTOXICITY

SUMMARY

Amitraz was tested for genotoxic potential both *in vitro* and *in vivo*. Assays included the *Salmonella* gene mutation assay (Ames test), the host mediated assay, the L5178Y mouse lymphoma assay, tests for *in vitro* and *in vivo* chromosomal aberrations, a mouse dominant lethal assay, tests for DNA damage, and tests for morphological cell transformation. In the Ames test, amitraz was considered negative for mutation induction while 2,4-dimethylaniline (an amitraz metabolite) was positive. Genotoxic potential was indicated for amitraz and 2,4-dimethylaniline, in the mammalian cell

L5178Y mouse lymphoma assay. In the mouse dominant lethal assay, one study produced positive results while the other resulted in negative data. Both assays, however, contained deficiencies that inhibited interpretation. For all other tests, amitraz was considered negative for genotoxic potential.

1. Gene Mutation

a) Bacteria

Amitraz was tested for mutagenic potential in the *Salmonella typhimurium* gene mutation assay (Ames test) with tester strains TA98, TA100, TA1535, TA1537 and TA1538 (McGregor and Prentice, 1983). The test was conducted both in the presence and absence of metabolic activation (mouse liver). The test was conducted with half log concentrations ranging from 33.3 µg/plate to 10 mg/plate amitraz in acetone. Concentrations at or exceeding 333 µg/plate resulted in precipitation. An increase in the number of revertants (when compared to concurrent acetone controls) was indicated in tester strain TA1538, both in the presence and absence of metabolic activation. An increase was also detected in tester strain TA100 in the presence of metabolic activation. These increases in mutagenicity were not, however, reproducible in subsequent tests. DPR considered the study acceptable as a FIFRA guideline study.

Additional studies were conducted to evaluate the mutagenic potential of amitraz in *Salmonella* and *E. Coli* (Everest and Wilcox, 1976a and 1976b; Moriya, et al.,1983; and Zimmer, et al. 1977). No mutagenic potential was indicated for amitraz in any of these studies, however, due to inadequate documentation and or supporting data, DPR did not consider any of the studies acceptable under FIFRA guidelines. In the Zimmer, et al. study, 2,4-dimethylaniline (an amitraz metabolite), was considered positive for mutation induction.

Amitraz was reported to be negative for mutation induction in the Host Mediated Assay (Wilcox 1976, and Everest 1976). Both of these reports had insufficient documentation to support findings. DPR did not consider these studies acceptable under FIFRA guidelines.

b) Mammalian Cells

McGregor and Riach (1983a) reported an increase in mutation when 2,4-dimethylaniline, a metabolite of amitraz, was tested in the mouse lymphoma L5178Y (thymidine kinase) assay. Test article concentrations included 1, 3.3, 10, 33.3, 100, 200, 300, 333.3, 400, 500 and 600 µg/ml. A dose related increase in mutation frequency was detected in the presence of S-9 (mouse liver metabolic activation mixture). DPR considered this study acceptable under FIFRA guidelines.

McGregor and Riach (1984) also tested amitraz in the L5178Y mammalian cell mutation assay. The test was performed 4 times in the presence and absence of metabolic activation (Aroclor 1254 induced mouse liver S-9). Test concentrations ranged from 0.06 to 33 µg/ml. The study authors concluded that amitraz was not positive for mutation induction in the mouse lymphoma assay. After close evaluation of the data, however, a negative (non-mutagenic) conclusion could not be supported. In assay number 1, no evidence of mutagenic activity was noted. In assay numbers 2 and 3, mutagenic activity was indicated (i.e., in the presence and absence of metabolic activation, both an increase in mutation frequency (greater than 2-fold) and a corresponding increase in absolute mutant number were observed). In assay number 4, in the presence of metabolic activation, an increase in mutation frequency was noted, however, a corresponding increase in absolute mutant number was not detected. DPR considered the study acceptable under FIFRA guidelines.

On the basis of the reported findings, the mutagenic potential of amitraz in the mouse lymphoma assay can not be discounted. This is supported by the mutagenic potential indicated by the amitraz metabolite, 2,4-dimethylaniline in the mouse lymphoma assay in the presence of metabolic activation (McGregor and Riach, 1983a).

2. Structural Chromosomal Aberration

a) *In Vivo* cytogenetics

An amitraz metabolite (2,4-dimethylaniline) was tested for genotoxic activity in the mouse micronucleus test (Hounsell and Walker, 1983). The test article was administered, by gavage, to groups of male CD-1 mice at 0, 56.3, 112.5 or 225 mg/kg. No increases in micronuclei were reported; however, the study had a number of deficiencies that inhibited interpretation. These deficiencies included a lack of female data, no dose justification, a lack of appropriate sampling times, and the lack of scoring criteria. DPR did not consider the study acceptable under FIFRA guidelines.

b) *In Vitro* cytogenetics

Brooker, et al., (1988) reported on the ability of amitraz to induce chromosomal aberrations in cultured human lymphocytes. For this test, cultured human lymphocytes, stimulated to divide by the addition of phytohemagglutinin, were exposed to amitraz both in the presence and absence of a rat S-9 metabolic activation mixture. Dosages included 0, 5, 10, and 20 µg/ml in the absence of metabolic activation, and 0, 3, 15, and 30 µg/ml in the presence of activation. Twenty-two hours after treatment with the test article, mitotic activity was arrested by the addition of cholchicine. Cells were processed for scoring and examined for chromosomal damage. No evidence of an increase in chromosomal aberrations was reported. DPR considered the study acceptable under FIFRA guidelines.

c) Mouse Dominant Lethal Assay

Amitraz was tested for activity in female CFLP mice in a dominant lethal assay (Palmer and James, 1977a). Amitraz was administered orally to female mice for 5 consecutive daily dosages of 0, 12, or 50 mg/kg. Two days after withdrawal from treatment, animals were divided into four groups. The groups were mated with fertile males at intervals of five days. While the study did not demonstrate dominant lethal effects, the study had a number of deficiencies rendering it unacceptable for registration purposes. These deficiencies included the lack of test article purity, lack of dosing solution analysis, an inadequate number of females per group, and no justification for dose selection. DPR considered the study unacceptable under FIFRA guidelines, but possibly upgradable with submission of missing data.

Palmer and James (1977b) also tested amitraz for activity in the male mouse dominant lethal assay. In this assay, male CFLP mice were treated, by gavage, with 0, 12, or 50 mg/kg amitraz. In males, a dose-related effect on body-weight gain was observed. This involved an initial loss up to day 3 of dosing for the 12 mg/kg group, and a loss throughout the dosing period for the 50 mg/kg group. As for litter effects, a lower implantation rate ($p<0.05$) was observed at 50 mg/kg. At the fifth mating, a higher implantation rate ($p<0.01$) was reported at 12 mg/kg. The study had a number of deficiencies rendering it unacceptable for registration purposes. These deficiencies included the lack of test article purity, lack of dosing solution analysis, an inadequate, and no justification for dose selection. DPR considered the study unacceptable under FIFRA guidelines, but possibly upgradable with submission of missing data.

3. Other Genotoxic Effects

a) DNA Damage

McGregor and Riach (1983b) tested amitraz for potential to induce unscheduled DNA synthesis (UDS). Amitraz was tested in human embryonic lung fibroblasts for UDS induction at dosages that ranged from 0 to 300 µg/ml. The initial DPR review of this study concluded that the study was acceptable as a FIFRA guideline study. Net nuclear grain counts, however, were not reported (i.e., nuclear grain counts were not corrected for cytoplasmic grain counts).

Petzold et. al, (1977) used the alkaline elution assay to test amitraz and several of its metabolites for DNA damage potential. The metabolites tested included: N-(2,4-dimethylphenyl)-N'-methylformamidine (U-40,481); 2,4-dimethylformanilide (U-36,893); 2,4-dimethylaniline (U-54,915A); and 4-amino-3-methylbenoxic acid (U-54,914). Under the conditions of this study, no significant increase in single strand breaks was reported following exposure to amitraz or the examined metabolites. Due to a number of deficiencies, however, the study was considered unacceptable. The deficiencies included

incomplete documentation of procedures and no indication of test article purity. DPR considered the study unacceptable under FIFRA guidelines.

b) Morphological Cell Transformation

The amitraz metabolite 2,4-dimethylaniline was tested for its ability to induce morphological transformation in C3H/10T½ mouse embryo fibroblasts (McGregor, et al. 1984). The assay was performed both in the presence and absence of a mouse liver metabolic activation mixture (S-9). Concentrations tested included 0, 5, 10, and 20 µg/ml in of presence of S-9, and 0, 100, 200, and 400 µg/ml in the absence of S-9. From this study, it was concluded that 2,4-dimethylaniline does not induce morphological cell transformation in C3H/10T½ cells. DPR considered the study acceptable under FIFRA guidelines.

Amitraz was tested for its ability to induce morphological transformation in C3H/10T½ mouse embryo fibroblasts (McGregor and Riach, 1983c). The assay was performed both in the presence and absence of a mouse liver metabolic activation mixture (S-9). Concentrations tested included 0, 12.5, 25, and 37.5 µg/ml in of presence of S-9, and 0, 5, 10, and 15 µg/ml in the absence of S-9. Amitraz did not induce morphological transformation in this test. DPR considered the study acceptable under FIFRA guidelines.

F. REPRODUCTIVE TOXICITY

SUMMARY

Several studies were conducted to monitor the effects of amitraz on rat and mouse reproduction. In the rat, amitraz exposure was associated with an increase in the percentage of deaths and a prolonged estrus. In the mouse, amitraz exposure was associated with an increase in food consumption, a decrease in body weight, a prolongation of pro-estrus, and a shortening of diestrus. The NOEL for reproductive effects (1 mg/kg/day) was based on observations made in the rat dietary study (Sutton, 1973b).

1. Dietary Study (Rat)

The reproductive effects of amitraz on rats (10-12 males/group, and 20-24 females/group) were studied by Sutton (1973b). The test compound was administered to Wistar rats, in their diet, for three generations. Exposures were set at 0, 15, 50 and 200 ppm. Approximate dosages were, 0, 1.4, 4.7 and 18.2 mg/kg. Four days after birth, F_1 neonatal survival was only 48% in the 200 ppm group. This experimental group was terminated at the F_1 weaning. In the F_2 generation, between day 4 and 21, a dose-related increase in the percentage of deaths was observed (i.e., 25% at 0, 35% at 15 ppm, and 57% at 50 ppm). The DPR data review of this study concluded that the NOEL for this study was 15

ppm. Due to retrospective stability data that demonstrated a 30% loss of active ingredient per week, the NOEL of 1.4 mg/kg/day was adjusted to 1 mg/kg/day. DPR considered the study acceptable under FIFRA guidelines.

2. Additional Reproduction Studies

Merryman and Sutton (1972) reported that amitraz exposure results in prolonged estrus in Wistar rats. The test article was administered in the diet, at 200 ppm (approximately 20 mg/kg/day), over a period of 18 weeks to 20 animals per group (14 in the control group). The mean cycle length for controls was 4.3 day. For treated animals, the mean cycle length was 6.1 days. On the basis of this report, the LOEL was 20 mg/kg/day.

The effects of amitraz on the thymus gland and estrus cycle in mice were investigated by Brown et al. (1978). Twenty-four male and 52 female SPF CFLP mice were fed a diet containing 400 ppm amitraz (106 mg/kg/day for males and 136 mg/kg/day for females) for periods up to 18 and 33 weeks respectively. Reported chemical related effects included an increase in food consumption (29% for males and 43% for females) and a decrease in body weight gain (31% for males and 24% for females). At 400 ppm, foci of inflammatory cells accompanying necrotic liver cells were reported in 65% of the females (compared to 37% for controls). No effects on the thymus gland nor the estrus cycle were reported.

Amitraz was tested for effects on the estrus cycle and hormones in female B6C3F1 mice (Hounsell and Rush, 1984). Groups of 70 animals were fed diets containing 0, 25, 100, or 400 ppm amitraz for up to 28 weeks. Food consumption and weight gain were not monitored. A dose-related prolongation of pro-estrus and a shortening of diestrus was reported. Lower blood levels of progesterone and higher levels of dehydroepiandrosterone sulfate were reported for the 400 and 100 ppm groups. Lower prolactin levels were also reported for these two dose groups. On the basis of these effects the NOEL established by this study was 25 ppm.

F. DEVELOPMENTAL TOXICITY

SUMMARY

The teratogenic potential of amitraz was studied in rats and rabbits. In one unacceptable guideline study with rats, intrauterine growth retardation was reported. In a separate rat developmental study a NOEL of 15 mg/kg/day was based on an increase in the incidence of dilated ureters and bilaterally increased renal pelvic cavitation, both considered minor defects. In an unacceptable rabbit study, fetal malformations were detected at dosages of 1 mg/kg/day and higher. In another study, a developmental NOEL of 6 mg/kg/day was established, based on resorptions and abortions. On the basis of these studies, DPR considered the developmental effects of amitraz to be minor.

1. Gavage Study (Rat)

A study of the teratogenic potential of amitraz on Wistar rats (11 to 13 pregnant rats per group) was reported on by Sutton (1973c). Amitraz was administered by gavage on days 8-20 of gestation. Dosages for this study included 0, 1, 3, and 12 mg/kg/day. Noted effects included intrauterine growth retardation in the high dose group (a 9.6% reduction in males and an 8.3% reduction in females when compared to controls). This study was, however, considered unacceptable due to a number of deficiencies. These included the lack of an analysis of dosing solution, the absence of test article characterization, an insufficient number of animals tested, and inadequate soft tissue examinations. DPR considered the study unacceptable under FIFRA guidelines.

Sutton (1973d) also reported on the effects of amitraz on pregnancy, parturition and care of young rats. Amitraz was administered (orally) from day 1-of pregnancy until young were weaned at 21 days old. Dosages for this study included 0, 1, 3, and 12 mg/kg/day. No treatment related effects were reported. Due to study deficiencies, DPR considered the study unacceptable under FIFRA guidelines. Deficiencies included insufficient number of pregnant animals, dosage levels not justified, and lack of clinical observations.

Amitraz was tested for teratogenic activity in Sprague Dawley rats (McIntyre, 1987a). Groups of 24 mated rats were administered amitraz, by gavage, from day 6 to 15 of gestation. Dosages included 0, 7.5, 15, and 30 mg/kg/day. On day gestation 20, animals were killed and their uterine contents were examined. On the basis of decreased body weight gain in the 15 mg/kg/day group (23% when compared to controls), the maternal NOEL was 7.5 mg/kg/day. Developmental effects included a statistically significant ($p<0.01$) increase in the incidence of dilated ureters in the 30 mg/kg/day group (64.9% versus 46% in control animals) and a dose related increase in bilateral renal pelvic cavitation (2.9%, 4.0%, 5.7%, 7.1% for the 0, 7.5, 15, and 30 mg/kg/day groups, respectively). The increase in bilateral renal pelvic cavitation was statistically significant ($p<0.05$) at the 15 mg/kg/day dose point. Both the dilated ureters and bilateral renal pelvic cavitation were considered minor effects. DPR considered the developmental NOEL to be 15 mg/kg/day. No major malformations or other developmental toxicity was attributed to treatment. DPR considered the study acceptable under FIFRA guidelines.

2. Gavage Studies (Rabbit)

Amitraz was tested for teratogenic activity in New Zealand white rabbits (Sutton, 1973e). Groups of 8-10 pregnant rabbits were given amitraz, by oral intubation, from day 6 to 18 of gestation. Dosages included 0, 1, 5, and 25 mg/kg/day. Abnormalities were noted in all dose groups. These included hydramnios (excessive amniotic fluid) and gastroschisis (opening in the abdominal wall) in the high dose group; cleft palate, meningocele associated with small ears, and a

displaced toe in the 5 mg/kg/day group; and one fetus without a lower incisor in the low dose group. Due to a number of deficiencies, however, this study was considered unacceptable to DPR as a FIFRA guideline study. The deficiencies included the lack of test article characterization, the lack of dosing solution analysis, an inadequate number of number of animals, and a concurrent respiratory disease. DPR was unable to assess a NOEL.

Another rabbit teratology study was reported by McIntyre (1987b). Three groups of 16 mated female New Zealand rabbits were given amitraz by gavage from day 7 to 19 of gestation. Dosages included 0, 3, 6 and 12 mg/kg/day. Maternal effects included polypnea and squinting in all treated groups, and weight loss followed by reduced weight gain in the 12 mg group (while controls gained 4% between days 7 and 13, and 5% between days 13 and 19, the high dose group lost 2% and gained 1% for the same periods). Developmental effects included 2 abortions and 3 total litter resorptions at 12 mg/kg/day. The maternal NOEL was < 3 mg/kg/day based on toxicity observed at all doses. On the basis of abortions and resorptions, the developmental NOEL for this study was 6 mg/kg/day. It is not known if the developmental effects were related to maternal toxicity. DPR considered this study acceptable as a FIFRA guideline study.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

1. Acute Toxicity

The acute toxicity of amitraz has been evaluated in rats, mice, guinea pigs, rabbits, dogs, baboons, and humans (see acute toxicity section in Toxicology Profile). Clinical signs associated with acute exposure of laboratory animals to amitraz include: central nervous system depression, ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. The acute toxicity of amitraz in laboratory animals was presented in TABLE I. On the basis of lethality after oral exposure, the most sensitive animals were dogs and baboons. These animals were at least 4 times more sensitive than rats, mice, and guinea pigs. Clinical signs or symptoms reported in humans exposed to amitraz included: paleness, dry mouth, drowsiness, slurred speech, disorientation, and loss of consciousness (Campbell, 1984). These effects were observed following a single oral dose of 0.25 mg/kg. No significant effects have been reported in humans at doses up to 0.125 mg/kg (Cass, 1992).

Acute effects were also noted in sub-chronic and chronic studies conducted with beagles (Patton and Williams, 1973; and Morgan et al., 1983). In the first study, a 90-day toxicity study, all animals given 4 mg/kg/day (highest dose tested) exhibited signs of CNS depression, vomiting, and ataxia 3 hours after dosing (see sub-chronic section of toxicology profile). In the second study, a chronic toxicity study, all animals in the 1.0 mg/kg/day group (highest dose tested) exhibited slight CNS depression 3 hours after dosing on days 1 and 2. The severity of the CNS response in the second study could not be determined, as the specific clinical signs were not reported.

On the basis of the results reported in laboratory animals and humans, the NOEL used to calculate a margin of safety for acute human exposure to amitraz was **0.125 mg/kg**.

2. Sub-Chronic Toxicity

Toxic effects associated with sub-chronic exposure were indicated in a variety of studies (see sub-chronic section of toxicology profile). The most prevalent effects included decreased body weight gain and CNS depression. In a 90-day toxicity study conducted with dogs, CNS depression and catarrhal conjuctivitis were reported at doses of 0.25 mg/kg/day and greater (Patton and Williams, 1973). A DPR review of the study concluded that the effects reported at 0.25 mg/kg/day were not considered to be of toxicological significance. On the basis of the study report and the DPR review, the NOEL was for this study was estimated to be **0.25 mg/kg/day**. This NOEL was used in calculating sub-chronic (seasonal) margins of safety in this risk assessment.

3. Chronic Toxicity

The toxic effects of chronic exposure to amitraz were investigated in a rat dietary study for toxicity and oncogenicity, a dietary oncogenicity study with mice, and an oral toxicity study with dogs. Reported effects included CNS depression (specific signs not reported), depressed growth rate, a reduction in food intake, liver hyperplastic nodules, and hyperkeratosis of the forestomach. The "CNS" effects were considered a response to acute exposure as they were observed 3 hours after dosing. On the basis of hyperplastic nodules in the livers of females, and hyperkeratosis of the forestomach in males (in B6C3F1 mice), a LOEL of 2.3 mg/kg/day was established for chronic toxicity. An estimated NOEL of **0.23 mg/kg/day** was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10 (U.S. EPA, 1987c).

4. Oncogenicity

An association between dietary exposure to amitraz and an increased incidence of tumors in mice was indicated.

Dietary exposure of CFLP mice to 400 ppm (84.4 mg/kg/day) amitraz has been associated with increases in lymphoreticular tumors. Lessor increases in lung tumors in females and liver tumors in both sexes were also detected. The initial scoring of the lymphoreticular tumors indicated a statistically significant response. Subsequent evaluations by different pathologists all confirmed the increase, but differed in the incidence of tumors. Using Fisher's exact comparisons, p values ranged from 0.0002 to 0.178 for the tumor incidence in the high-dose group. Due to the inconsistency of the subsequent evaluations, DPR used the original evaluation for quantitative assessment.

In B6C3F1 mice, females exhibited an increase in benign and/or malignant hepatocellular tumors at 400 ppm. The increase was statistically significant, and exceeded historical bounds. A dose-related increase in liver hyperplastic nodules was also evident. In males at 400 ppm, pulmonary adenomas were statistically increased above controls, and also exceeded historical bounds.

The oncogenic potency was estimated using the default assumption that a threshold dose does not exist for an oncogenic effect. The dose-response relationship from the dose range used in the animal studies was extrapolated to the low dose range generally experienced by humans using a linearized multistage (LMS) mathematical model. The model is constrained to linearity in the low dose region. The "potency" is defined as the maximum likelihood estimate (MLE or Q_1) of the linear term in the model equation and/or its upper 95% confidence limit (upper bound or Q_1*). The potency estimated from animal data is then scaled to humans. The current DPR default approach in interspecies dose scaling is to assume dose equivalence between animals and humans based on a 3/4 power of the body weight (BWt). Therefore, potency in the unit of $(mg/kg/day)^{-1}$ derived animal data is extrapolated to humans by a factor of $(BWt_{human}/BWt_{animal})^{1/4}$. On the basis of assumed body weights of 76

kg and 30 g for humans and mice, respectively, the scaling factor used for this assessment was 7.09. Risk is then calculated as the potency multiplied by the exposure or dose. It is an estimate of the excess cumulative probability of tumor occurrence in a lifetime (70 years for humans). Cancer potency for amitraz was estimated using the "Global86" computer software (Howe, 1986). On the basis of the lymphoreticular tumors in CFLP female mice (Burnett, et al., 1976), the Q_1 was 4.34×10^{-3} $(mg/kg/day)^{-1}$. The upper bound (Q_1*) on the Q_1 was 7.84×10^{-3} $(mg/kg/day)^{-1}$. These values were then adjusted for inter-species variability assuming a body weight to the 3/4 power proportionality. The adjusted Q_1 was 3.08×10^{-2} $(mg/kg/day)^{-1}$ and the adjusted upper bound was 5.56×10^{-2} $(mg/kg/day)^{-1}$ The United States EPA considered amitraz a potential carcinogen and calculated an upper bound on potency of 4.97×10^{-2} $(mg/kg/day)^{-1}$ (U.S. EPA, 1994).

5. Other Effects

Studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Genotoxic potential was indicated for 2,4-dimethylaniline (an amitraz metabolite) in bacteria (Ames test) and mammalian cells grown *in vitro* (L5178Y mouse lymphoma assay) while amitraz exhibited mutagenic potential only in the mouse lymphoma assay. In the mouse dominant lethal assay, one study produced positive results while the other resulted in negative data. For all other tests, amitraz was considered negative for genotoxic potential.

B. EXPOSURE ASSESSMENT

1. Occupational Exposure

Work related exposure to amitraz was evaluated by the Worker Health and Safety branch of DPR (Haskell, 1994). Exposure scenarios considered for this assessment included treatment of pears, cotton, and livestock. Job activities considered included mixing, loading, applying, harvesting, flagging, and field checking. Pear application was assumed to involve application with an air-blast sprayer. Cotton application was assumed to be by aerial or ground application.

Safety clothing required when mixing, loading, or applying products containing amitraz includes a protective suit with long-sleeves and long pants, chemical resistant gloves, hat, boots and goggles or face shield. A helmet with visor may be substituted for the hat and goggles during aerial application. Mixer/loaders should also wear a chemical resistant apron when handling the concentrated product.

TABLE XII presents dosage estimates for single day (absorbed daily dosage, ADD), seasonal (seasonal average daily dosage, SADD), annual (annual average daily dosage, AADD) and lifetime (lifetime average daily dosage, LADD) occupational-related exposures to amitraz.

Estimated ADDs for pear treatment were based on biomonitoring data with amitraz (discussed in Haskell, 1994). A report on the urinary excretion of amitraz metabolites for workers applying Mitac® WP indicated an average value of 0.51 mg (Hacker, 1992). In a study conducted by Cambell and Needham (1984), it was determined that 82% of radio-labeled amitraz was excreted in the urine of adult males after 72 hours. To correct for the percentage of radio-labeled material that may have been excreted in the feces or lost due to processing, the 0.51 mg from the Hacker study was divided by 0.82. Furthermore, the 8 loads processed in the Hacker study is assumed to be 57% of a full days work (Castro and Ramos, 1988). The dosage estimate was, therefore, adjusted accordingly. Using the same process for the high, low, and average estimates, the calculated absorbed daily dosage, ranged from 3.1 to 25.7 µg/kg/day for a "mixer-loader-applicators" (MLA) with a mean value of 14.4 µg/kg/day (see TABLE XII for mean and maximum values). These values were based on an assumed body weight of 76 kg.

For pear harvesters, the potential dermal exposure was based on dislodgeable foliar residues (DFR) and a transfer factor (TF). The DFR is the amount of residue available for exposure and the transfer factor provides an estimate of the amount of foliage contacted per hour for workers hand-harvesting pears in an amitraz treated orchard. The average (DFR 0.63 µg/cm^2) was calculated by Haskell (1993) and was based on an amitraz study by Brady (1992). The actual DFR range from the Brady study was 0.60 to 0.80 µg/cm^2. The TF used was 4,023 cm^2/hr and was based on a study involving the use of propargite on pears and nectarines. The average dermal exposure estimate was, therefore, 20.3 mg/person/8 hour (DFR times TF times 8). The assumed dermal absorption (13.8%) was based on a study in rat (Stewart, 1993, reported by Haskell, 1994). On the basis of an assumed negligible inhalation exposure and a body weight of 76 kg, the average ADD of amitraz to pear harvesters was estimated to be 36.9 µg/kg/day with a maximum ADD of 46.7 µg/kg/day.

TABLE XII: Estimation of absorbed daily dosages (acute, seasonal, annual, and lifetime) of Amitraz for workers in pear orchards, cotton fields, and those involved with the treatment of livestock.

	Dosage (mg/kg/day)[a]			
Worker	**ADD[b]**	**SADD[c]**	**AADD[d]**	**LADD[e]**
Pears				
Mixer/Loader/Applicator	14.4 (25.7)	2.4	0.39	0.21
Harvester	36.9 (46.7)	22.1	3.64	1.94
Cotton				
Ground				
Mixer/Loader/Applicator	7.2 (11.5)	1.0	0.32	0.17
Air				
Mixer/Loader	21.1 (35.6)	1.4	0.46	0.25
Pilots	11.3 (17.4)	0.8	0.25	0.13
Flaggers	13.1 (29.6)	0.9	0.29	0.15
Field Checkers	7.2 (8.1)	0.5	0.22	0.12
Cattle				
Mixer/Loader/Applicator	1.1 (4.6)	0.01 (0.16)	0.01 (0.16)	0.005 (0.084)
Swine				
Mixer/Loader/Applicator	2.1 (0.5)	0.30 (0.07)	0.30 (0.07)	0.16 (0.038)

a For pears and cotton, values were based on the mean and maximum (in parentheses) potential exposure. Maximum exposure for pear workers and cotton field checkers (cotton scouts) was based on the range. Maximum values for cotton mixer/loaders, pilots and flaggers were based on two standard deviations above the mean. The number of samples was 10 for mixer/loaders and 11 for pilots and flaggers. For pears and cotton, maximum estimates were only considered for acute exposure. For cattle, values were based on small and large (in parentheses) operations. For swine, values were based on average and corporate size (in parentheses) farms. Dermal absorption was assumed to be 13.8% (Stewart, 1993)

b Absorbed Daily Dosage was based on 76 kg body weight for all job classifications except field checkers (54.8 kg). Data source for field checkers included females.

c Seasonal Average Daily Dosage was based on 10 exposure days per season for pear mixer/loader/applicators, 36 days per season for pear harvesters, 8 days per season for cotton mixer/loaders (air application), pilots and flaggers, 16 days for cotton mixer/loaders/applicators (ground application), and 11 days per season for cotton scouts (field checkers). The potential seasonal exposure days for cattle was 3.3 and 12.5 days for small and large operations, respectively. For swine, the potential treatment days was assumed to be 52. The usage season for pears was assumed to be 60 days. The usage season for cotton was assumed to be 120 days. The usage season for livestock was assumed to be all year (SADD = ADD x exposure days ÷ days per season).

d Annual Average Daily Dosage was based on the number of exposure days per year divided by days in a year (AADD pears and cotton = ADD x exposure days ÷ 365; AADD for livestock = SADD).

e Lifetime Average Daily Dosage was based on 40 years employment and a 75 year life (i.e., LADD = AADD x 40 ÷ 75).

TABLE XII also presents the values for cotton treatment. Cotton can be treated with amitraz either by ground application or by aircraft (Haskell, 1994). For ground application, values were based on surrogate exposure data with oxydemeton-methyl to vegetables (Oshita et. al, 1986, discussed by Haskell 1994). For aerial application, values were based on surrogate exposure data with tributyl phosphorotrithioate (DEF) (Haskell, 1994). Estimated average dosages for daily dermal exposure were; 7.2, 21.1, 11.3, 13.1, and 7.2 µg/kg for mixer/loaders/applicators (ground), mixer/loaders (air), pilots, flaggers and field checkers, respectively. In addition to the mean values, TABLE XII also presents the maximum values for acute exposure. These values were; 11.5, 35.6, 17.4, 29.6, and 8.1 µg/kg for mixer/loaders/applicators (ground), mixer/loaders (air), pilots, flaggers and field checkers, respectively. For field checkers, the maximum values were based on the highest value of the calculated range. The maximum values for all other cotton related occupations were calculated as two standard deviations above the mean. Except for field checker estimates, values were based on the default body weight of 76 kg. The data used to estimate exposure to field checkers was assumed to be either male or female. The assumed body weight for field checkers was, therefore, 54.8 kg.

As indicated in TABLE XII, the calculated ADDs were 1.1 and 4.6 µg/kg for small and large cattle operations, respectively. For average and corporate size farms, the values for swine were 2.1 and 0.5 µg/kg, respectively.

The SADD was determined by multiplying the number of expected exposure days times the ADD, and dividing by the number of days in a season. The days in a season were 60 for pears, 120 for cotton, and 365 for livestock. For mixer/loader/applicators treating pears, the number of potential exposure days was assumed to be 10. For pear harvesters, potential exposure days was assumed to be 36. Sixteen potential exposure days were assumed for mixer/loader/applicators involved with ground application of amitraz on cotton. Eight potential exposure days was assumed for mixer/loaders, pilots and flaggers involved with aerial application of amitraz on cotton. The number of potential exposure days assumed for cotton scouts was 11. With livestock, assumed potential exposure days were 3.3 days for small cattle operations, 12.5 days for large cattle operations, and 52 days for swine. On the basis of these assumptions, SADDs based on average exposures ranged from 0.01 to 22.1 µg/kg/day. The job category with the highest exposure was pear harvesters.

The AADD was determined by multiplying the number of expected exposure days times the ADD and dividing by the number of days in a year (i.e., 365). Expected exposure days were the same as those used in the seasonal calculations. On the basis of these assumptions, average AADDs ranged from 0.01 to 3.64 µg/kg/day. The job category with the highest exposure was pear harvesters.

The LADD for each job activity was based on an expected 40 year employment and a 75 year life span. Calculated LADDs based on average exposures

ranged from 0.005 to 1.94. The job category with the highest exposure was pear harvesters.

2. Dietary Exposure

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

a) Residue Data

The sources of residue data for dietary exposure assessment include DPR and federal monitoring programs, field trials, and survey studies. In the absence of data, surrogate data from the same crop group as defined by U.S. EPA or theoretical residues equal to U.S. EPA tolerances are used. Residue levels that exceed established tolerances (over-tolerance) are not utilized in the dietary exposure assessment because over-tolerance incidents are investigated by the DPR Pesticide Enforcement Branch and are relatively infrequent. DPR evaluates the potential risk from consuming commodities with residues over tolerance levels using an expedited acute risk assessment process.

DPR has four major sampling programs: (1) priority pesticide, (2) preharvest monitoring, (3) produce destined for processing, and (4) marketplace surveillance. The priority pesticide program focuses on pesticides of health concern as determined by DPR Enforcement and Medical Toxicology Branches. Samples are collected from fields known to have been treated with the specific pesticides. For the marketplace surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. The sampling strategies for both priority pesticide and marketplace surveillance are similar and are weighted toward such factors as pattern of pesticide use; relative number and volume of pesticides typically used to produce a commodity; relative dietary importance of the commodity; past monitoring results; and extent of local pesticide use. The preharvest monitoring program routinely examines the levels of pesticides on raw agricultural commodities in the field at any time during the growth cycle. Generally, these data are not used unless the application schedule is known and residue data are not available from other monitoring programs. Commodities destined for processing are collected in the field no more than 3 days prior to harvest, at harvest, or post-harvest before processing.

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

The U. S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. Several states, including California, collect samples at produce markets and chain store distribution centers close to the consumer level. The pesticide and produce combinations are selected based on the toxicity of the pesticide as well as the need for residue data to determine exposure. In addition, USDA is responsible for the National Residue Program that provides data for potential pesticide residues in meat and poultry. These residues in farm animals can occur from direct application, or consumption of commodities or by-products in their feed.

No monitoring data is currently available for amitraz residues in meat (cattle and swine) cotton, milk, or honey. Priority monitoring for amitraz residues in pears was conducted by DPR in 1988 and 1990. For both years the minimum detection limit was approximately 0.2 ppm. The report indicated that out of 25 treated samples, amitraz was detected in 3 samples, with the highest detected value being 0.4 ppm. The actual application rate for the monitoring data is, however, unknown. With the exception of honey, residue values for this risk assessment were based on registrant supplied field studies. Amitraz residues for honey were based on the U.S. EPA tolerance. The values used are presented in TABLE XIII. Maximum values were assumed for acute exposure while average values were used for chronic exposures.

TABLE XIII: Summary of residue values for amitraz used in the dietary risk assessment.

Commodity	Residue (ppm) Acute	Chronic	Data Source
Cattle			
(fat)	0.01	0.005	field study[a,b]
(meat)	0.01	0.005	field study[a,b]
(meat by-products)	0.01	0.005	field study[a,b]
(milk)	0.019	0.019	field study[b,c]
(milk fat)	0.095	0.095	field study[b,c]
Cotton Seed	1.0	0.29	field study[d,e,f,g,h,i]
Honey	1.0	1.0	EPA tolerance[j]
Pears			
(raw)	1.66	0.73	field study[i,k,l]
(cooked)	0.14	0.14	field study[m]
Poultry			
(eggs)	0.01	0.005	field study[n]
(fat)	0.01	0.005	field study[n,o]
(meat)	0.01	0.005	field study[n,o]
(meat by-products)	0.01	0.005	field study[n,o]
Swine			
(fat)	0.01	0.005	field study[p]
(meat)	0.01	0.005	field study[p]
(meat by-products)	0.01	0.005	field study[p]

a Ford, 1982a; b, Hughes 1974; c, Ford, 1982b; d, Brady and Castro, 1990; e, Castro, 1987a; f, Castro, 1987b; g, Castro, 1988a; h, Castro, 1988b; i, Manley 1989; j, U.S. EPA, 1993; k, Brady, 1992; l, Paul and Vukich, 1994; m, Dynamac, 1994; n, Manley and Snowdon, 1988; o, Needham and Hemmings, 1988; p, Ford, 1984.

Registrant supplied field study data indicates that average and maximum amitraz residues in raw pears are 0.73 and 1.66 ppm, respectively (Brady, 1992).

The residue values for fat, meat, and meat by-products reported for cattle were 0.01 and 0.005 ppm for average and maximum estimates, respectively (Ford, 1982a; and Hughes, 1974). The residue values for fat, meat, and meat by-products reported for swine were 0.01 and 0.005 ppm for average and maximum estimates, respectively (Ford, 1984).

Residue values for milk and milk fat were assumed to be 0.019 and 0.095 ppm, respectively (Hughes, 1974; and Ford, 1982b). Due to the limitations of the data, acute and chronic values were assumed to be the same.

For cottonseed, average residues, based on registrant supplied field study data were 0.29 ppm (Brady and Castro, 1990; Castro, 1987a; Castro, 1987b; Castro, 1988a;

Castro, 1988b; and Manley 1989). Maximum amitraz residues in cottonseed exceeded the U.S. EPA tolerance for that commodity (1.0 ppm)(U.S. EPA, 1993). Residue values that are greater than established tolerances, are not utilized in the DPR dietary exposure assessments, as they are the subject of other actions by regulatory agencies. The tolerance value of 1.0 ppm was, therefore, used to assess acute exposure to amitraz from cottonseed.

For poultry, residue information was obtained from studies provided by the registrant. The average residue value reported for eggs, fat, meat, and meat by-products was 0.01 ppm (Manley and Snowdon, 1988). The maximum value reported was 0.005 ppm.

For honey, U.S. EPA Tolerances were used as a conservative estimate of expected residue values.

b) Acute Exposure

Estimates of potential acute (daily) dietary exposure use the highest measured residue values at or below the tolerance for each commodity. The following assumptions were used to estimate potential acute dietary exposure from measured residues: 1) the residue does not change over time, 2) the concentration of residue does not decrease when the raw agricultural commodity (RAC) is washed, 3) processing of RACs into various food forms does not reduce the residue, and 4) all foods that are consumed will contain the highest reported residue.

Acute dietary exposure analyses were conducted using the Exposure-4™ computer program developed by Technical Assessment Systems, Inc. (TAS, 1992a). This software estimates the distribution of single-day exposures for the overall U.S. population and specific population sub-groups. The analysis utilizes food consumption data, as reported by the U.S. Department of Agriculture (USDA, 1988). Exposure-4™ is designed to evaluate exposure to chemical residues as a function of consumer-days. A consumer-day is any day in which at least one commodity is consumed.

On the basis of the 95th percentile of user-day exposures for the population subgroups examined, the potential acute dietary exposure of amitraz, from pears, meat, milk, cotton seed, eggs, poultry and honey ranged from 0.4 to 2.3 µg/kg (see TABLE XIV for summary data). The population sub-group with the largest potential dosage (2.3 µg/kg/day) was "non-nursing infants less than 1 year of age".

TABLE XIV: Potential acute dietary exposure to amitraz from residues in pears, meat, milk, cotton seed, eggs, poultry and honey.

Population Sub-group	Dosage (µg/kg body wt/day)[a,b]
U.S. Population	1.0
Western Region - U.S. Population	1.0
Nursing Infants (<1 year)	0.9
Non-Nursing Infants (<1 year)	2.3
Females (13+/P[c]/NN[d])	0.5
Females (13+N[e])	0.6
Children (1-6 years)	2.0
Children (7-12 years)	1.2
Males (13-19 years)	0.6
Females (13-19 years/NP[f]/NN)	0.6
Males (20+ years)	0.5
Females (20+/NP/NN)	0.4
Seniors (55+ years)	0.5
U.S. Population (16+ years)	0.5

a = Exposure is evaluated as a function of user-days (i.e., day which at least one commodity containing amitraz is consumed).
b = Values represent the 95th percentile of consumer-day exposure.
c = pregnant
d = not nursing
e = nursing
f = not pregnant

As indicated, the above dietary exposure estimates were based on consumer-day exposure, i.e., an individual's response to the survey was used if he or she consumed one of the commodities on the day in question. When multiple commodities are being considered, individuals with the highest exposure from a single commodity may not be in the upper percentile of exposure for the other

commodities. This can result in an apparent decrease in overall exposure when compared to single commodity exposures, i.e., the exposure estimates from multiple commodity exposures will tend to move in the direction of the average rather than the maximum exposures. The combined result, therefore, may be significantly less than estimates based on a single commodity. With this in mind, dietary exposure to amitraz from pears only was also evaluated. Pears have been emphasized due to the relatively high predicted residue levels (at least an order of magnitude greater than predicted for meat or milk).

On the basis of the 95th percentile of user-day exposures for the population subgroups examined, the potential acute dietary exposure of amitraz, from pears only, ranged from 1.4 to 15.3 μg/kg/day (TABLE XV). The population sub-group with the largest potential exposure (15.3 μg/kg/day) was children age 1 to 6 years of age.

c) Subchronic Exposure

In addition to the estimated acute exposure values, TABLE XV presents subchronic exposure estimates. These values were obtained from the 50th percentile of user-day exposures from the Exposure-4™ dietary software. Exposure-4™ software was chosen because it addresses only users, while Exposure-1™ (chronic) includes non-users. In this risk assessment, it is assumed that an individual is unlikely to receive the maximum single day exposure every day of a multiple exposure scenario. The 50th percentile, therefore, was chosen as a default. The subchronic dietary exposure estimates will be discussed in the dietary component of the combined occupational and dietary seasonal exposures.

On the basis of the 50th percentile of user-day exposures for the population subgroups examined, the potential acute dietary exposure of amitraz, from pears only, ranged from 0.1 to 2.9 μg/kg/day (TABLE XV). The population sub-group with the largest potential exposure (2.9 μg/kg/day) was females age 13 plus, who were nursing.

TABLE XV: Potential acute and subchronic dietary exposure to amitraz from residues in pears.

Population Sub-group	Dosage (µg/kg body wt/day)[a]	
	Acute[b]	Subchronic[c]
U.S. Population	6.0	0.2
Western Region - U.S. Population	5.7	0.2
Nursing Infants (<1 year)	1.4	0.6
Non-Nursing Infants (<1 year)	2.3	0.6
Females (13+/P[d]/NN[e])	4.8	2.4
Females (13+N[f])	6.8	2.9
Children (1-6 years)	15.3	0.2
Children (7-12 years)	7.5	0.1
Males (13-19 years)	4.6	0.1
Females (13-19 years/NP[g]/NN)	4.4	0.1
Males (20+ years)	4.4	0.2
Females (20+/NP/NN)	5.1	0.2
Seniors (55+ years)	5.4	0.2
U.S. Population (16+ years)	5.0	0.2

a = Exposure is evaluated as a function of user-days (i.e., day which at least one commodity containing amitraz is consumed).
b = Values represent the 95th percentile of consumer-day exposure.
c = Values represent the 50th percentile of consumer-day exposure.
d = pregnant
e = not nursing
f = nursing
g = not pregnant

d) Chronic (annual) Exposure

Estimates of potential dietary exposure used the average of measured and "below detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to one-half (50%) of the minimum detection limit (MDL) for each commodity. The following assumptions were used to estimate potential chronic dietary exposure from measured residues: 1) the residue level does not change over time, 2) residues are not reduced by washing the raw agricultural commodity (RAC), 3) processing is assumed to be at a level equivalent to the RAC residue level that may be multiplied by an adjustment factor, and 4) exposures to a commodity at

all reported residue levels do occur, i.e., a commodity with the average calculated residue is consumed every day at an annual average level (dosage).

The potential chronic dietary exposure was calculated using the Exposure-1™ computer program developed by TAS (Technical Assessment Systems, Inc., 1992b). The food consumption data for the chronic analysis was also based on the 1987-88 United States Department of Agriculture Nationwide Food Consumption Survey (USDA, 1988). The program estimates the annual average exposure for all members of a designated population subgroup.

The annual average potential chronic dietary exposure to amitraz from pears, meat, milk, cotton seed, eggs, poultry and honey, for the U.S. population, was 0.22 µg/kg/day (see TABLE XVI for summary data). The population sub-group with the highest potential exposure (0.7 µg/kg/day) was children ages 1 to 6.

TABLE XVI: Potential chronic dietary exposure to amitraz from residues in pears, meat, milk, cotton seed, eggs, poultry and honey.

Population Sub-group	Dosage (µg/kg body wt/day)[a]
U.S. Population	0.22
Western Region - U.S. Population	0.24
Nursing Infants (<1 year)	0.09
Non-Nursing Infants (<1 year)	0.55
Females (13+/P[b]/NN[c])	0.18
Females (13+N[d])	0.19
Children (1-6 years)	0.70
Children (7-12 years)	0.41
Males (13-19 years)	0.23
Females (13-19 years/NP[e]/NN)	0.18
Males (20+ years)	0.14
Females (20+/NP/NN)	0.13

a = Exposure estimates were based on daily consumption averaged over 365 days.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

Since chronic exposure estimates are based on average daily exposure rather than the 95th percentile, multiple commodity exposures are not expected to be less than predicted for exposure through a single commodity (see discussion

under acute exposure). This is illustrated by the comparison of exposures from pears, meat, milk, cotton seed, eggs, poultry and honey (see TABLE XVI) with exposure estimate from pears only (TABLE XVII).

TABLE XVII: Amitraz dosage following potential chronic (annual) dietary exposure from pears only.

Population Sub-group	Dosage (µg/kg body wt/day)[a]
U.S. Population	0.01
Western Region - U.S. Population	0.01
Nursing Infants (<1 year)	0.01
Non-Nursing Infants (<1 year)	0.05
Females (13+/P[b]/NN[c])	0.03
Females (13+N[d])	0.02
Children (1-6 years)	0.03
Children (7-12 years)	0.02
Males (13-19 years)	0.01
Females (13-19 years/NP[e]/NN)	0.01
Males (20+ years)	0.01
Females (20+/NP/NN)	0.01

a = Exposure estimates are based on daily consumption, of a given commodity, averaged over 365 days.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

As indicated in TABLE XVII, the average potential chronic dietary exposure (from pears only), for the U.S. population, was 0.01 µg/kg/day. The population sub-group with the highest potential dietary exposure (0.05 µg/kg/day) was non-nursing infants less than 1 year of age.

3. Combined Exposure (Occupational and Dietary)

In an effort to predict total potential exposure to agricultural workers using amitraz, a combined exposure estimate was calculated by adding the estimated occupational and dietary exposures. These estimates are shown in TABLE XVIII. Estimates have been calculated for ADD, SADD, AADD, and LADD . The occupational component of exposure was presented in TABLE XII. For the ADD (acute exposure), the dietary component of exposure (5.0 μg/kg/day) was based on the 95th percentile of acute exposure for the United States population age 16 and above (see TABLE XV). For the SADD, the dietary component was 0.2 μg/kg/day and was based on the 50th percentile of the acute daily dosage, to the U.S. population age 16 years and older (TABLE XV). The dietary components (0.22 μg/kg/day) for both the combined AADD and the LADD were based on the annual average daily dosage, to the U.S. population (TABLE XVI). The lifetime dietary component of the combined LADD was assumed to be the same as the annual average daily dosage. This implies that an individual would consume the same annual average level for 75 years.

TABLE XVIII: Estimation of combined occupational and dietary absorbed daily dosages (daily, seasonal, annual, and lifetime) of Amitraz for workers in pear orchards, cotton fields, and those involved with the treatment of livestock.

	Dosage (mg/kg/day)			
Worker	**ADD[a,b]**	**SADD[c]**	**AADD[d]**	**LADD[e]**
Pears				
Mixer/Loader/Applicator	19.4 (30.7)	2.6	0.61	0.43
Harvester	41.9 (51.7)	22.3	3.86	2.16
Cotton				
Ground				
Mixer/Loader/Applicator	12.2 (16.5)	1.2	0.54	0.39
Air				
Mixer/Loader	26.1 (40.6)	1.6	0.68	0.47
Pilots	16.3 (22.4)	1.0	0.47	0.35
Flaggers	18.1 (34.6)	1.1	0.51	0.37
Field Checkers	12.2 (13.1)	0.7	0.44	0.34
Cattle				
Mixer/Loader/Applicator	6.1 (9.6)	0.21 (0.36)	0.23 (0.38)	0.23 (0.30)
Swine				
Mixer/Loader/Applicator	7.1 (5.5)	0.50 (0.27)	0.52 (0.29)	0.38 (0.26)

a For pears and cotton, values were based on the mean and maximum (in parentheses) potential occupational exposure combined with dietary exposure (see TABLEs XII & XV). Maximum estimates were only considered for acute exposure. For cattle, values were based on small and large (in parentheses) operations. For swine, values were based on average and corporate size (in parentheses) farms.

b Occupational absorbed daily dosage is shown in TABLE XII. The dietary component (5.0 μg/kg/day) was based on the 95th percentile of acute exposure for the United States population age 16 and older (see TABLE XV).

c Occupational seasonal average daily dosage is shown in TABLE XII. The dietary component (0.2 μg/kg/day) was based on the 50th percentile of potential acute exposure for the United States population age 16 and older (TABLE XV).

d Occupational annual average daily dosage is shown in TABLE XII. The dietary component was 0.22 μg/kg/day (TABLE XVI).

e Occupational lifetime average daily dosage is shown in TABLE XII. The dietary component (0.22 μg/kg/day) was the same as that used for annual average daily dosage.

a) Acute Exposure

As indicated in TABLE XVIII, the combined (occupational and dietary) ADD estimates for average amitraz exposure ranged from 6.1 to 41.9 μg/kg/day. When estimated dosage was based on maximum potential exposure, the range was 5.5 to 51.7 μg/kg/day. The job classification with the highest potential exposure was pear harvesters.

b) Seasonal Exposure

For seasonal exposure (60 days for pears, 120 days for cotton, and 365 days for livestock), the combined SADD estimates for amitraz exposure ranged from 0.21 to 22.3 μg/kg/day (TABLE XVIII). The job classification with the highest potential exposure was pear harvesters.

c) Annual Exposure

The combined AADD estimates for amitraz exposure ranged from 0.23 to 3.86 μg/kg/day (TABLE XVIII). The job classification with the highest potential exposure was pear harvesters.

d) Lifetime Exposure

The combined lifetime average daily dosage (LADD) estimates for amitraz exposure ranged from 0.23 to 2.16 μg/kg/day (TABLE XVIII). The job classification with the highest potential exposure was pear harvesters.

C. RISK CHARACTERIZATION

In order to characterize the potential risks associated with exposure to amitraz, margins of safety (MOSs), were calculated for both occupational and dietary exposures. An MOS is defined as the ratio of the No-Observed-Effect-Level (NOEL) to the absorbed dosage. Experimentally determined NOELs were described in the Toxicology Profile and Hazard Identification sections of this document. Estimates of absorbed dosages were established in the Exposure Section. In general, a margin of safety equal to or greater than 10 is considered adequate for the protection of human health when it is based on NOELs from human studies. When exposure is based on NOELs from non-human mammalian studies, an additional factor of 10 is generally used (i.e., MOS of 100). Margins of safety for acute exposure were based on human data. Margins of safety for seasonal, and annual, exposure, however, were based on NOELs from non-human mammalian data (i.e., a dog study for seasonal and a mouse study for annual and life-time exposures). Since lifetime exposure estimates were lower than those for annual exposure (TABLE XII), and margin of safety calculations for annual and lifetime use the same NOEL, all MOSs for lifetime exposure will be greater than annual exposure MOSs. Since all calculated annual margins of safety were greater than 100

(except for pear harvesters), calculations were not performed for lifetime exposures (the margin of safety for pear harvesters exposed over a lifetive was greater than 100). For oncogenic end points, risk estimates were also calculated for potential lifetime occupational, dietary and combined exposures.

1. Occupational Exposure

TABLE XIX: Calculated margins of safety (MOS) for potential daily, seasonal, and annual exposure to amitraz for workers in pear orchards, cotton fields, and those involved with the treatment of livestock.

	Margin of Safety[a]		
Worker	**Daily (acute)[b]**	**Seasonal[c]**	**Annual[d]**
Pears			
Mixer/Loader/Applicator	9 (5)	100	590
Harvester	3 (3)	11	63
Cotton			
Ground			
Mixer/Loader/Applicator	17 (11)	260	730
Air			
Mixer/Loader	6 (4)	180	500
Pilots	11 (7)	330	930
Flaggers	10 (4)	290	800
Field Checkers	17 (15)	520	1,100
Cattle			
Mixer/Loader/Applicator	110 (27)	25,000 (1,600)	23,000 (1,500)
Swine			
Mixer/Loader/Applicator	60 (250)	840 (3,500)	770 (3,200)

[a] Margin of Safety defined as the no observed effect level (NOEL) divided by the estimated dosage. Dosages were presented in TABLE XII. NOELs were discussed in the Hazard Identification section. Values in parentheses represent margins of safety based on maximum exposures. All values less than 10 have been rounded to the nearest whole number; all other values have been rounded to two significant digits.

[b] Daily (acute) exposure. The NOEL used was 0.125 mg/kg/day, based on CNS effects observed in humans.

[c] Seasonal exposure. The estimated NOEL used was 0.25 mg/kg/day, based on CNS depression and catarrhal conjuctivitis in dogs.

[d] Annual exposure. The NOEL used was 0.23 mg/kg/day, based on hyperplastic nodules, and hyperkeratosis of the forestomach in mice.

a) Acute Exposure

As indicated in the TABLE XIX, estimated margins of safety for daily (acute) exposure, for the various job categories examined, ranged from 3 to 110 when based on average potential exposure. When margins of safety were based on maximum potential exposure, values ranged from 3 to 250. Job categories with margins of safety less than 10 included pear mixer/loader/applicators, pear harvesters, cotton mixer/loaders (involved with the aerial application of amitraz), pilots, and flaggers.

b) Seasonal Exposure

The estimated margin of safety for seasonal exposure for pear harvesters was 11. For all other job categories examined, margins of safety were at least 100.

c) Annual Exposure

The estimated margin of safety for annual exposure for pear harvesters was 63. For all other job categories examined, margins of safety were at least 100.

d) Life-time Exposure

(1) Non-Oncogenic Toxicity

Since lifetime exposure estimates were lower than those for annual exposure (TABLE XII), and margin of safety calculations for annual and lifetime use the same NOEL, all MOSs for lifetime exposure will be greater than annual exposure MOSs. Since all calculated annual margins of safety (except for pear harvesters) were greater than 100, margins of safety for life-time average daily dosage, for the various job categories examined, were assumed to be greater than 100. For pear harvesters, the LADD was 1.94 μg/kg/day. The corresponding MOS is 120.

(2) Oncogenicity

For carcinogenic end-points, life-time cancer risks associated with occupational exposure to amitraz were estimated by multiplying the expected dosage by the maximum likelihood estimate (Q_1) or the upper bound (Q_1*) of the potency slope Q_1*. The estimated dosages for life-time occupational exposures were presented in TABLE XII. The calculated Q_1 was 3.08×10^{-2} $(mg/kg/day)^{-1}$. The calculated Q_1* was 5.56×10^{-2} $(mg/kg/day)^{-1}$ (see hazard identification section). Cancer risk estimates for occupational exposure to amitraz through the use on pears, cotton, or livestock, based on the Q_1 of the potency slope, ranged from 1.5×10^{-7} to 6.0×10^{-5} . Cancer risk estimates, based on the Q_1* of the potency slope ranged from 2.7×10^{-7} to 1.1×10^{-4}

2. Dietary Exposure

a) Acute (daily) Exposure

Margins of safety for potential acute dietary exposure to amitraz were calculated by taking the ratio of the experimentally determined NOEL (i.e., 0.125 mg/kg body weight, based on CNS effects observed in humans) to the potential dietary dosage. The values presented in TABLE XV reflect the potential dietary exposure from pears at the 95th percentile. As indicated, in TABLE XX, margins of safety ranged from 8 to 89. Children ages 1 to 6 had a margin of safety less than 10. All other population sub-groups had margins of safety greater than 10.

TABLE XX: Calculated margins of safety (MOS) for potential acute dietary exposure to amitraz from pear consumption.

Population Sub-group	MOS[a]
U.S. Population	21
Western Region - U.S. Population	22
Nursing Infants (<1 year)	89
Non-Nursing Infants (<1 year)	54
Females (13+/P[b]/NN[c])	26
Females (13+N[d])	18
Children (1-6 years)	8
Children (7-12 years)	17
Males (13-19 years)	27
Females (13-19 years/NP[e]/NN)	28
Males (20+ years)	28
Females (20+/NP/NN)	25
Seniors (55+ years)	23
U.S. Population (16+ years)	25

a = Margin of safety defined as the NOEL divided by the estimated dosage. The NOEL used for acute exposure was 0.125 mg/kg based on CNS effects in humans. All values less than or equal to 10 have been rounded to the nearest whole number. All values greater than 10 have been rounded to 2 significant digits.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

b) Subchronic Exposure

Inasmuch as subchronic exposure to amitraz was estimated for agricultural workers using the pesticide, an estimate of subchronic dietary exposure was needed to determine total amitraz exposure potential. The dietary component of subchronic exposure was 0.2 µg/kg/day (50th percentile of user-day exposures for the United States population age 16 and older)(TABLE XV). Based on an estimated NOEL of 0.25 mg/kg (CNS depression and catarrhal conjuctivitis observed in dogs). A calculated margin of safety for this exposure would be 1,300.

c) Chronic (annual) Exposure

Margins of safety for annual dietary exposures were based on an estimated NOEL of 0.23 mg/kg (liver hyperplastic nodules, and hyperkeratosis of the forestomach observed in mice at 2.3 mg/kg). The exposure values were presented in the exposure section of this document (TABLE XVI). As indicated in TABLE XXI, calculated margins of safety were greater than 100 for all population sub-groups evaluated.

TABLE XXI: Calculated margins of safety (MOS) for potential annual exposure to amitraz from pears, meat, milk, cotton seed, eggs, poultry, and honey.

Population Sub-group	MOS[a]
U.S. Population	1,000
Western Region - U.S. Population	960
Nursing Infants (≈1 year)	2,600
Non-Nursing Infants (≈1 year)	420
Females (13+/P[b]/NN[c])	1,300
Females (13+N[d])	1,200
Children (1-6 years)	330
Children (7-12 years)	560
Males (13-19 years)	1,000
Females (13-19 years/NP[e]/NN)	1,300
Males (20+ years)	1,600
Females (20+/NP/NN)	1,800

a = Margin of safety defined as the NOEL divided by the estimated dosage. The NOEL used for chronic exposure was 0.23 mg/kg/day based on liver hyperplastic nodules, lung adenomas and hyperkeratosis of the forestomach in mice. All values have been rounded to 2 significant digits.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

d) Lifetime Exposure (Oncogenicity)

For oncogenic end-points, life-time cancer risks associated with dietary exposure to amitraz from pears, meat, milk, cotton seed, eggs, poultry, and honey, were estimated by multiplying the expected average lifetime dosage by the maximum likelihood potency estimate (Q_1) or the upper bound on the maximum likelihood potency estimate for cancer induction (Q_1*). The estimated average lifetime dosage was 0.22 μg/kg/day for U.S. population (TABLE XVI). The calculated Q_1 was 3.08×10^{-2} $(mg/kg/day)^{-1}$ and the calculated Q_1* was 5.56×10^{-2} $(mg/kg/day)^{-1}$ (see hazard identification section). The resulting theoretical risks to the U.S. population were 6.8×10^{-6} and 1.2×10^{-5} for the Q_1 and Q_1*, respectively.

3. Combined (Occupational and Dietary) Exposure

TABLE XXII: Calculated margins of safety (MOS) for potential combined daily, seasonal, and annual exposure to amitraz for workers in pear orchards, cotton fields, and those treating livestock (including both occupational and dietary exposures).

	Margin of Safety[a]		
Worker	**Daily (acute)[b]**	**Seasonal[c]**	**Annual[d]**
Pears			
Mixer/Loader/Applicator	6 (4)	96	380
Harvester	3 (2)	11	60
Cotton			
Ground			
Mixer/Loader/Applicator	10 (8)	220	430
Air			
Mixer/Loader	5 (3)	160	340
Pilots	8 (6)	260	490
Flaggers	7 (4)	230	450
Field Checkers	10 (10)	370	530
Cattle			
Mixer/Loader/Applicator	20 (13)	1,200 (700)	1,000 (610)
Swine			
Mixer/Loader/Applicator	18 (23)	500 (920)	440 (790)

[a] Margin of Safety defined as the no observed effect level (NOEL) divided by the estimated dosage. Dosages were presented in TABLE XVIII. NOELs were discussed in the Hazard Identification section. All values less than or equal to 10 have been rounded to the nearest whole number; all other values have been rounded to two significant digits.

[b] Daily (acute) exposure. The NOEL used for ADD was 0.125 mg/kg/day, based on CNS effects observed in humans.

[c] Seasonal exposure. The estimated NOEL used for SADD was 0.25 mg/kg/day, based on CNS depression and catarrhal conjuctivitis in dogs.

[d] Annual exposure. The NOEL used for AADD was 0.23 mg/kg/day, based on liver hyperplastic nodules, and hyperkeratosis of the forestomach in mice.

a) Acute Exposure

As indicated TABLE XXII, estimated margins of safety for absorbed daily dosage (acute), for the various job categories examined, ranged from 3 to 20 when based on average expected exposure. When margins of safety were based on maximum potential exposure, margins of safety ranged from 2 to 23. Mixer/loader/applicators for pears, pear harvesters, mixer/loaders (involved with aerial application of amitraz to cotton), pilots, and flaggers all had estimated margins of safety less than 10.

b) Seasonal Exposure

The estimated margins of safety for seasonal average daily dosage (based on occupational and dietary exposure), for pear mixer/loader/applicators was 96. For harvesters, the margin of safety was 11. All other estimated margins of safety for job categories involved with the use of amitraz were greater than 100.

c) Annual Exposure

The estimated margins of safety for annual average daily dosage (based on occupational and dietary exposure), for pear harvesters was 60. For all other job categories examined, the margins of safety were greater than 100.

d) Lifetime Exposure (Oncogenicity)

For carcinogenic end-points, life-time cancer risks associated with occupational and dietary exposure to amitraz were estimated by multiplying the LADD by the Q_1 or the Q_1*. The estimated dosages for life-time combined (occupational and dietary) exposures were presented in TABLE XVIII. The calculated Q_1 was 3.08 x 10^{-2} $(mg/kg/day)^{-1}$. The calculated Q_1* was 5.56 x 10^{-2} $(mg/kg/day)^{-1}$ (see hazard identification section). The resulting theoretical cancer risks to the U.S. population are presented in TABLE XXIII.

TABLE XXIII: Estimated life-time cancer risk estimates following occupational and dietary exposure to amitraz from pears, meat, milk, cotton seed, eggs, poultry, and honey.

Lifetime Cancer Risk Estimates[a]		
Worker	**Risk**	
	Q_1	**Q_1***
Pears		
Mixer/Loader/Applicators	1.3×10^{-5}	2.4×10^{-5}
Harvesters	6.7×10^{-5}	1.2×10^{-4}
Cotton		
Ground		
Mixer/Loaders/Applicators	1.2×10^{-5}	2.2×10^{-5}
Air		
Mixer/Loaders	1.4×10^{-5}	2.6×10^{-5}
Pilots	1.1×10^{-5}	2.0×10^{-5}
Flaggers	1.2×10^{-5}	2.1×10^{-5}
Field Checkers	1.0×10^{-5}	1.9×10^{-5}
Cattle		
Mixer/Loader/Applicators		
Small Operations	6.9×10^{-6}	1.3×10^{-5}
Large Operations	9.4×10^{-6}	1.7×10^{-5}
Swine		
Mixer/Loader/Applicators		
Average Size Farms	1.2×10^{-5}	2.1×10^{-5}
Corporate Size Farms	8.0×10^{-6}	1.4×10^{-5}

a Life-time cancer risk estimated by multiplying combined occupational and dietary LADD by the Q_1 or the Q_1*.

As indicated in the table, cancer risk estimates based on the Q_1 range from 6.9×10^{-6} to 6.7×10^{-5}. Cancer risk estimates based on the Q_1* range from 1.3×10^{-5} to 1.2×10^{-4}.

V. RISK APPRAISAL

A health risk assessment was conducted for the potential exposure of amitraz to agricultural workers and to the general public from dietary sources (pears, poultry, cotton products, meat, meat byproduct, milk, and honey). The routes of exposure considered were dermal and inhalation for occupational and oral for dietary. For occupational exposure, daily, seasonal, annual, and life-time exposure conditions were considered. For dietary exposure, acute (daily), subchronic and chronic exposure scenarios were considered. Additionally, combined potential exposures from occupational and dietary sources were addressed.

Risk assessment is the process used to evaluate the potential for human exposure to a substance and the likelihood that the potential exposure will cause adverse health effects in humans under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to the prediction of potential risk to the human population. This makes it necessary for certain assumptions and extrapolations to be incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in a level of uncertainty in the risk characterization. Qualitatively, risk assessments for all chemicals have similar uncertainties. The degree or magnitude of the uncertainty, however, can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. One of the primary assumptions, which is inherent in all risk assessments using animal data is that effects observed in laboratory animals represent expected effects in humans at comparable dosages. In the absence of actual human data, this assumption and resulting extrapolation are necessary. Areas of uncertainty specific to this risk assessment are delineated in the following discussion.

An area of primary interest is the evidence for carcinogenic activity of amitraz in the CFLP and B6C3F1 mouse studies. Dietary exposure to amitraz was associated with statistically significant increases in lymphoreticular tumors in female CFLP mice, as well as lessor increases for lung tumors in females and liver tumors in both sexes. Increased hepatocellular tumors were also present in female B6C3F1 mice, reaching statistical significance for adenomas, carcinomas, and for combined adenoma and carcinomas. Additionally, a dramatic increase in apparently pre-neoplastic hyperplastic nodules of the liver was present in females, while increased tumor incidences in three organ systems (lymph, liver, and lung), two strains of mice (CFLP and B6C3F1), and/or both sexes. The similarity of effects in two separate experiments greatly adds to the weight of evidence for amitraz oncogenicity. The U.S. Environmental Protection Agency has also classified amitraz as a carcinogen suitable for quantitative risk assessment, establishing a cancer potency value of 0.0497 (U.S. EPA, 1994)

In the dietary assessment, residue estimates were based on field trials and tolerance values. These field studies were conducted to establish tolerances for specific raw agricultural commodities and, therefore, were designed to obtain the highest potential residue under the conditions indicated on the product label. With pears, the assumed residue (1.66 ppm) was based on a field study (maximum allowable use). Monitoring was conducted with this commodity, however, the data were inadequate. Out of 25 treated samples, amitraz was detected in 3 samples, with the highest detected value being 0.4 ppm. The actual application rate, however, was not known. Without this key

bit of information, the data cannot be interpreted. When field study data were inadequate or non-existent, residue values were assumed to be present at tolerance levels. Furthermore, it was assumed that residue levels were stable; i.e., residue values do not change over time, the concentration does not decrease when the commodity is washed, the residue concentration is not reduced by processing of the commodity, and all consumed commodities contain the highest reported residue. The resulting estimates of exposure based on these assumptions were most likely overestimates of the actual exposure from dietary sources. On the basis of the current data base, quantification of this overestimate is not currently considered possible.

For occupational exposure, a number of extrapolations and assumptions were necessary. Estimated dosages for pear treatment were based on a urinary excretion study with amitraz (Hacker, 1992). These data indicated an average exposure of 0.51 mg/day. In an independent study conducted by Cambell and Needham (1984), urinary excretion was shown to account for 82% of the radio-labeled amitraz after 72 hours. To account for potential loss in feces or due to sample processing, the value from the Hacker study was divided by 0.82. Furthermore, the number of amitraz loads considered in the Hacker study was assumed to be only 57% of a full days work. The dosage estimate was, therefore, adjusted accordingly (i.e., to 100% of a work day). For pear harvesters, the potential dermal exposure was based on dislodgeable foliar residues (DFR) and a transfer factor (TF). The DFR being the amount of residue available for exposure and the TF a function of the actual work practices and resulting physical contact. The DFR was based on an actual amitraz study. The TF was based on a study involving the use of propargite on pears and nectarines. In spite of the chemical differences, the application rates and physical activities (involved in the performance of the job) were assumed to be the same for the propargite study and the proposed use of amitraz. Inhalation exposure for harvesters was assumed to be negligible. For cotton treatment, exposures were based on surrogate exposure data from a study with tributyl phosphorotrithioate (DEF). Exposure values for amitraz were estimated by adjusting the DEF values for differences in application rates. For cotton scouts, exposure was estimated using a transfer factor (TF) obtained from surrogate data from studies with activities considered to be similar to the proposed amitraz usage. The DFR was assumed from a study with pear foliage. Since application rates were different (1.5 lbs active ingredient per acre on pears and 0.94 lbs active ingredient for cotton), the exposure was adjusted (see Haskell, 1994). While the values used were considered the best available information, uncertainties are inherent whenever extrapolations from surrogate data are used to estimate exposure. These uncertainties can result in either over or under estimates of the subsequent risk to workers.

In addition to the dermal and inhalation routes from occupational exposure, dietary exposure was evaluated in order to estimate a combined potential exposure for the various occupational activities. The dietary component was based on a national consumption survey conducted by the U.S. Department of Agriculture. The exposure data used in the acute dietary assessment of workers was restricted to those survey

respondents age 16 years and older. This assumes that the number of workers under this age is too small to influence the interpretation of the analysis. Furthermore, inherent in the use of the national survey is the assumption that the result is representative of California residents.

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

A tolerance is the maximum, legal amount of a pesticide residue that is allowed on a raw or processed agricultural commodity, or in an animal tissue used for human consumption. The U.S. EPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g., improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to non-approved commodities). Tolerances are enforced by the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies (e.g., Pesticide Enforcement Branch of DPR).

Current pesticide tolerances are generally set at levels that are not expected to produce deleterious health effects in humans from chronic dietary exposure. The data requirements for establishing a specific tolerance include: 1) toxicology data for the parent compound, major metabolites, degradation products and impurities, 2) product chemistry, 3) analytical methods(s) that are readily available, accurate and precise, 4) measured residues in crops used for animal feeds, 5) measured residues in animal tissues (e.g., meat, milk, and eggs) from direct or indirect (feed) applications, 6) measured residue levels from field studies. The minimum requirements for the field study include: 1) an application rate at or above the highest rate on the product label, 2) the greatest number of allowable repeat applications, 3) the shortest pre harvest interval listed on the product label. Generally, the registrant of the pesticide requests a commodity-specific tolerance, which is equal to the highest measured residue, or some multiple of that value, from the field trial using the specific pesticide.

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides." In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance" As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population sub-groups can be calculated from the product of the tolerance and the daily consumption rate.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. The TAS Exposure-4™ software program and the USDA consumption data base are used in the assessment. The acute tolerance assessment does not routinely address multiple commodities at tolerance levels since the probability of consuming multiple commodities at these levels decreases as the number of commodities included in the assessment increases.

A dietary exposure assessment for amitraz exposure was conducted using tolerance levels as assumed residue values. TABLE XXIV shows the calculated margin of safety

(MOS) range for each label approved commodity. As indicated, the highest tolerance level and the lowest MOS is for pears. The potential dosages from acute dietary exposure to amitraz, from pears, ranged from 8.5 to 51 µg/kg/day. Corresponding MOSs ranged from 2 to 15. The population sub-group with the largest theoretical dosage and smallest MOS (51 µg/kg/day and 2) was "non-nursing infants less than 1 year of age".

TABLE XXIV: Amitraz tolerances and corresponding margins of safety (MOSs) for acute dietary exposure.

Commodity	Tolerance (ppm)	Margins of Safety[a] (Range)
Cattle meat	0.05	391-893
Cattle meat by-product	0.30	N/A
Cattle fat	0.10	868-2551
Cotton seed	1.00	351-1008
Eggs	0.01	2016-8333
Honey	1.0	81-4467
Pears	3.00	2-15
Poultry-meat	0.01	1524-4310
Milk	0.03	36-272
Milk fat	0.30	93-694
Swine meat	0.05	360-1471
Swine Meat by-product	0.30	N/A
Swine Fat	0.10	977-2976
Swine Liver	0.20	N/A

a Based on human acute NOEL of 0.125 mg/kg (Cambell, 1984; Cass, 1992) and residues at tolerance levels.
N/A Not available due to inadequate population sample size for evaluation

C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations or commodities was not conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from CDFA pesticide monitoring programs that indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990).

VII. CONCLUSIONS

The toxicology data base for amitraz has indicated potential adverse effects in human and laboratory animal studies. Effects reported after acute exposure to the pesticide have generally been associated with the central nervous system. Studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Chronic exposure to amitraz has been associated with an increased incidence of oncogenicity in mice. The genotoxicity data base indicates that amitraz and 2-4-dimethylaniline (a primary plant metabolite and an intermediate mammalian metabolite of amitraz) have mutagenic potential.

Several occupational activities associated with the agricultural use of amitraz, and one population sub-group potentially exposed to amitraz through the diet, have margins of safety less then the values conventionally considered to be protective of human health. In these cases, mitigation should be considered to reduce potential exposure.

Cancer risk estimates for occupational exposures (including dietary) to amitraz through the use on pears, cotton, or livestock, and non-occupational exposures via consumption of commodities treated with amitraz, were between 1 and 12 in 100,000. For dietary exposure only, cancer risk estimates were between 7 and 12 in 1,000,000.

An additional assessment of acute risk potential based on U.S. EPA tolerances indicates that margins of safety based on current U.S. EPA set tolerance levels are less then the values conventionally considered to be protective of human health.

VIII. REFERENCES

Anon, 1981. **Summary of topical (ocular and dermal) studies with BAAM® EC/Mitac ® EC and BAAM® 50W/Mitac® WP in animals and man**. The Upjohn Company. DPR DOCUMENT 287-25,31 #984422.

Brady, S.S. 1981. **Determination of amitraz-derived dislodgeable residues on pear foliage following two applications of Mitac® WP 14 days PHI.** DPR DOCUMENT 287-084 #119685.

Brady, S.S. and L. Castro, 1990. **Total residues of Amitraz® and its major metabolites at harvest in cottonseed treated with Ovasyn**, USA 1988. NOR-AM Company study R122.01.88. DPR DOCUMENT 287-094-121865.

Brady, S.S., 1992. **At-Harvest residues of Amitraz® in or on pears resulting from two applications of Mitac® EC or Mitac® WP using both a 14-day and a 30-day interval between applications USA and Canada, 1991**. NOR-AM Company study L-91R-01. DPR volume 287-106-132498.

Berczy, Z.S., R. Binns, and A.J. Newman, 1972. **Acute inhalation toxicity of the rat of BTS 27-419**. Huntington Research Centre. DPR DOCUMENT 287-012 #984504.

Brooker, P.C., L.C. Akhurst, and V.M. Gray, 1988. **Technical Amitraz Metaphase Chromosome Analysis of Human Lymphocytes Cultured In Vitro.** Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron Walden Essex. DPR Document 287-072 #74559.

Brehm, M., 1987. **The Photodegredation of Amitraz**. Schering Agrochemicals Ltd. Schering Code # ZK 49974. DPR Document 287-061 #65466.

Brehm, M., 1988. **The Photolysis of Amitraz**. Schering Agrochemicals Ltd. Schering Code # ZK 49974. DPR Document 287-061 #65467.

Bright, A.A.S., 1987. **Determination of the Vapor Pressure of Amitraz**. Schering Agrochemicals Limited. Report Number CHEM/87/78. DPR Document 287-056 #59724.

Bright, A.A.S., and A.M. Stalker, 1987a. **Amitraz: Determination of the Partition Coefficient Between N-Octanol and Water at 25`C**. Schering Agrochemicals Limited. Report Number CHEM/87/87. DPR Document 287-056 #59725.

Bright, A.A.S., and A.M. Stalker, 1987b. **Amitraz: Solubility in Water at 25`C**. Schering Agrochemicals Limited. Report Number CHEM/87/74. DPR Document 287-056 #59726.

Bronzan and Jones, 1989. **Assembly bill 2161, Addition to the Food and Agriculture Code SEC 8 section 13060**. California Food and Agriculture Code, Sacramento, CA.

Brown, D.J., R. Brunett, J. Crowley, P.C. Cryer, M.C. Lancaster, and G.J. Trunbull, 1978. **Amitraz: Investigation of Effects on the Thymus Gland and Oestrous Cycle in Mice**. Boots. DPR Document 287-042 #1107.

Burnett, R., J. Crowley, B. Lessel, D.S.G. Patton, M.M. Sutton, G.J. Trunbull, and G.A.H. Williams, 1976. **BTS 27 419: 80-Week Carcinogenicity Study in Mice - Final Report**. Study report submitted in support of new pesticide product registration, The Upjohn Company, Kalamazoo, Michigan, Report # TX76039. DPR Document 287-011 #984561.

Campbell, J.K., 1984. **A Comparison of the Metabolism of 14C-Amitraz in Rat, Mouse, Baboon, and Human**. FBC Limited, Chesterford Park Research Station, Report Number METAB/84/1. DPR Document 287-041 #1101.

Campbell, J.K., and D. Needham, 1984. **Urinary Excretion of (14C)-Amitraz by Two Male Humans Following a Single Oral Dose of 0.25 mg/kg Body weight**. FBC Limited, Chesterford Park Research Station, Report Number METAB/84/10. DPR Document 287-041 #24646.

Cass, L.M.R., 1992. **Report of a Double Blind Tolerance Study of Amitraz in Six Adult Healthy Volunteers**. Schering Agrochemicals LTD, Study Number RD197/20170. DPR Document 287-084 #119687.

Castro, L., and Ramos, M., 1988. **Exposure of Spray operator to Amitraz During Air Blast Application of Mitac WP to Pear Trees**. DPR Document 287-069 #70554.

Castro, L., 1987a. **Total residues of Amitraz® and metabolites in cottonseed following early and midseason application of Mitac EC in trials run in the USA in 1985 and 1986**. NOR-AM Company study 12005. DPR Document 287-058 #121850.

Castro, L., 1987b. **Total residues of Amitraz® and metabolites in cottonseed following late season application of Mitac EC in trials run in the USA in 1985 and 1986**. NOR-AM Company study 12007. DPR Document 287-058 #121852.

Castro, L., 1988a. **Effects of processing on total residues of Amitraz®, BTS 27271, and BTS 27919 in ginned cottonseed from trials conducted in the USA in 1987**. NOR-AM Company study 12017. DPR Document 287-093 #121858.

Castro, L., 1988b. **Total terminal residues of Amitraz® and its major metabolites in ginned cottonseed resulting from application of Mitac EC in trials conducted in the USA in 1987**. NOR-AM Company study 12016. DPR Document 287-092 #121855.

CDFA, 1983. **Summary of Reports from Physicians of Illnesses that were Posssibly Related to Pesticide Exposure During the Period of January 1 - December 31, 1982 in California.** HS-1098, California Department of Food and Agriculture, Worker Health and Safety Branch.

CDFA, 1984. **Summary of Reports from Physicians of Illnesses that were Posssibly Related to Pesticide Exposure During the Period of January 1 - December 31, 1983 in California.** HS-1186, California Department of Food and Agriculture, Worker Health and Safety Branch.

CDFA, 1985. **Summary of Reports from Physicians of Illnesses that were Posssibly Related to Pesticide Exposure During the Period of January 1 - December 31, 1984 in California.** HS-1304, California Department of Food and Agriculture, Worker Health and Safety Branch.

CDFA, 1986. **Summary of Reports from Physicians of Illnesses that were Posssibly Related to Pesticide Exposure During the Period of January 1 - December 31, 1985 in California.** HS-1370, California Department of Food and Agriculture, Worker Health and Safety Branch.

CDFA, 1987. **Summary of Illnesses and Injuries Reported in California by Physicians as Potentially Related to Pesticides - 1986.** HS-1418, California Department of Food and Agriculture, Worker Health and Safety Branch.

CDFA, 1990. **Residues in Fresh Produce-1989**. California Department of Food and Agriculture, Pesticide Enforcement Branch, Sacramento, CA.

Colley, J., S. Dawe, R. Heywood, A.E. Street, W.A. Gibson, and C. Gopinath, 1983. **Amitraz 104 Week Tumorigenicity Study in Mice**. Boots, HRC, and FBC Report # TOX/83/179-93. DPR Document 287-036 #1090.

Chassis, I.R., 1990. **Dermal absorption of amitraz in the rat**. Schering Agrochemicals Limited, Project ID TOX/90/179-178, Nor-Am Chemical Company. DPR Document 287-084 #119678.

Corbett, J.R., K. Wright, and A.C. Baillie, 1984. **The Biochemical Mode of Action of Pesticides**, Second Edition, Academic Press.

DPR, 1993a. **Pesticide Use Report; Annual 1991**. State of California Environmental Protection Agency, Department of Pesticide Regulation, Information Services Branch, Sacramento, CA.

DPR, 1993b. **Summary of Illnesses and Injuries Reported by California Physicians as Potentially Related to Pesticides - 1990.** HS-1666, California Department of Food and Agriculture, Worker Health and Safety Branch, March 1993.

DPR, 1994a. **Pesticide Use Report; Annual 1992**. State of California Environmental Protection Agency, Department of Pesticide Regulation, Information Services Branch, Sacramento, CA.

DPR, 1994b. **Pesticide Illness Surveillance Program Summary Report - 1991.** HS-1692, California Department of Food and Agriculture, Worker Health and Safety Branch, May 26, 1994.

Dynamac Corporation, 1994. **Residue search for Amitraz and Pears.** Dynamac Corporation Pesticide Residues Information Service, NATIONAL FOOD PROCESSORS ASSOCIATION - 1991. Dynamac Search ID: 1642.018. Performed for Agrevo, Tuesday July 19, 1994.

Edmiston, S., and D. Richmond, 1988. **California Summary of Illness and Injury Reported by Physicians as Potentially Related to Pesticides - 1987.** HS-1493, California Department of Food and Agriculture, Worker Health and Safety Branch, September 1988.

Ernst, G.F., E. Mattern, H. Mol, R. Kommerid, and F.W. van der Kreek, 1983. **The presence of Amitraz residues in dairy milk after one dermal treatment with TAKTIC® in Holland**. Hercules, Inc. DPR Document 287-061 #63318.

Everest, R.P., 1976. **BTS 27 419, Mutagenicity Study in the Male Mouse Perivisceral Cavity Host-Medicated Assay.** Submitted by The Upjohn Company in support of registration. DPR Document 287-12 #984574.

Everest, R.P., and P. Wilcox, 1976a. **BTS 27 419, BTS 27 271, BTS 27 919 and BTS 28 369: Mutagenicity Testing in Bacterial In Vitro Systems.** Submitted by The Upjohn Company in support of registration. DPR Document 287-12 #984574.

Everest, R.P., and P. Wilcox, 1976b. **BTS 27 419: Mutagenicity Testing Against Salmonella Typhimurium Strains TA1535, TA1537 and TA1538 in the Presence and Absence of Liver Microsomes from Male and Female Mice.** Submitted by The Upjohn Company in support of registration. DPR Document 287-74 #75276.

FDA, 1981. **Amitraz**. In: the FDA Surveillance Index for pesticides, Vol 1. U.S. Food and Drug Administration, Washington, D.C.

Ford, J.J., 1982a. **Amitraz resides in selected tissues following a dip-vat treatment of dairy cattle with TAKTIC® EC**. Hercules, Inc. DPR Document 287-061 # 63315.

Ford, J.J., 1982b. **Amitraz resides present in the milk and butterfat of dairy cows treated with TAKTIC® EC**. Hercules, Inc. DPR Document 287-061 # 63317.

Ford, J.J., 1984. **Tissue residue study following dermal spray applications of Amitraz (TAKTIC® formulation) to swine**. Nor-Am Chemical Co., Inc. DPR Document 287-061 # 63321.

Glenn, M.W., and R.W. Neilsen, 1975. **U-36059 - Oral LD_{50} in rats with 21.4% EC formulation containing propylene oxide**. The Upjohn Company. DPR Document 287-008 #984456.

Hall, 1973. **Skin irritancy of formulation SN 6554 containing 20% 27 419**. Data submitted with application for new pesticide product registration for BAAM EC miticide/insecticide. The UpJohn Company. DPR Document 287-012 (page T-2271).

Hacker, L.A., 1992. **Monitoring of the Metabolites of Amitraz in Urine of Spray Operators Applying Mitac WP to Pear Trees in Washington.** DPR Document 287-084 #119686.

Haskell, D., 1993. **Estimation of Exposure of Persons in California to Pesticide Products that Contain Amitraz.** Exposure analysis in response to request for registration of amitraz, California Environmental Protection Agency, Department of Pesticide Regulation, Worker Health and Safety Branch, Sacramento, California.

Herr, R.R., 1979. **Presentation to the Scientific Advisory Panel by the UpJohn Company: Pathologic Findings on the Matched Control and amitraz 400 ppm Females from the Boots 80 Week Mouse Study by Various Pathologists with Commentary**. Document submitted by Nor-Am Chemical Company and The UpJohn Company, in support of registration of Mitac, BAAM, and Taktic. DPR Document 287-043 #1126.

Hounsell, I.A., and K.C. Rush, 1984. **Technical Amitraz: The effects of dietary administration on the oestrous cycle and hormones in the mouse**. FBC Limited, Chesterford Park Research Station, Saffron Walden, Essex. Report Number TOX/84/179-97, DPR Document 287-042 #1109.

Hounsell, I.A., and A.K. Walker, 1983. **A Micronucleus Study in Mice Using BTS 24868 (2,4-dimethylaniline)**. FBC Limited, Chesterford Park Research Station, Saffron Walden, Essex. Report Number TOX/83/179-52, DPR Document 287-042 #1114.

Howe, R.B, K.S. Crump, and C. Van Landingham, 1986. **GLOBAL86 A Computer Program to Extrapolate Quantal Animal Toxicity Data to Low Doses**. Clement Associates, Inc., Ruston Louisiana.

Hughes, K.W., 1974. **Estimation of BTS 27419 and BTS 27271 in animal tissues and milk. NOR-AM Company study AX74018**. DPR Document 287-004 #984326.

Kakuk, T.J., 1978. **Pathologic Findings on the Matched Control and Amitraz 400 ppm Females from the Boots 80 Week Mouse Study by Various Pathologists**. The UpJohn Company. Report code number 315-78-9610-005, From presentation to the Scientific Advisory Panel. DPR Document 287-043 #1126.

Kakuk, T.J., 1979. **Four-hour acute inhalation study with BAAM® 50W in rats**. The UpJohn Company. DPR Document 287-033 #984499.

Knowles, C.O., and H.J. Benezet, 1981. **Excretion Balance, Metabolic fate and Tissue Residues Following Treatment of Rats with Amitraz and N'-(2,4-Dimethylphenyl)-N-Methylformamidine**. Journal of Environ. Sci. Health, 547-555. DPR Document 287-041.

Krieger R., and R. Rutz, 1992. **Exposure to Pestiide Mixer/Loaders and applicators in California.** Analysis of various handling Scenarios in California, California Environmental Protection Agency, Department of Pesticide Regulation, Worker Health and Safety Branch, Sacramento, California. HS-1656

Liggett, M.P., 1983a. **Irritant effects on rabbit skin of TAKTIC® EC**. FBC Ltd. DPR Document 287-060 #64176.

Liggett, M.P., 1983b. **Irritant effects on rabbit eye of TAKTIC® EC, formulation CR-15875**. FBC Ltd. DPR Document 287-060 #64175.

Manley, J.D., 1989. **Analytical method for the determination of combined residues of Amitraz® and metabolites hydrolysing to 2,4-dimethylaniline in various plant materials by gas chromatography (edition no. 3)**. Schering Agrochemicals Company study R64. DPR Document 287-089 #121846.

Manley, J.D. and P.J. Snowdon, 1988. **Amitraz® - derived residues containing the 2,4-dimethylaniline moiety in the tissues and eggs of laying hens following a 28-day feeding study in the UK, 1987**. NOR-AM Company study R266. DPR Document 287-071 #73437.

McGibbon, A.S., and I.D. Kelly, 1984. **Metabolism of [^{14}C]-Amitraz in Pears (an interim report).** FBC Report METAB/84/4. DPR Document 287-043 #1122.

McGregor, D.B., A.G. Brown, and C.G. Riach, 1984. **Technical BTS 24868 (2,4-Xylidene): Induction of Morphological Transformation in C3H/10T½ Cells.** Inveresk Research International, Report Number TOX/84/179-96. DPR Document 287-042 #1112.

McGregor, D.B., and R.D. Prentice, 1983. **Technical Amitraz: Ames Bacterial Mutagenicity Test.** Inveresk Research International, Report Number TOX/83/179-77. DPR Document 287-042 #1119.

McGregor, D.B., and C.G. Riach, 1983a. **Technical BTS 24868 (2,4-Xylidene): Mouse Lymphoma Mutation Assay.** Inveresk Research International, Report Number TOX/83/179-91. DPR Document 287-042 #1115.

McGregor, D.B., and C.G. Riach, 1983b. **Technical Amitraz: Unscheduled DNA Synthesis in Human Embryonic Cells.** Inveresk Research International, Report Number TOX/83/179-90. DPR Document 287-042 #1117.

McGregor, D.B., and C.G. Riach, 1983c. **Technical Amitraz: Induction of Morphological Transformation in C3H/10T½ Cells.** Inveresk Research International, Report Number TOX/83/179-78. DPR Document 287-042 #1113.

McGregor, D.B., and C.G. Riach, 1984. **Technical Amitraz: Mouse Lymphoma Mutation Assay.** Inveresk Research International, Report Number TOX/83/179-94. DPR Document 287-042 #1118.

McIntyre, M., 1987a. **T279 Technical Amitraz: Teratogenicity study in the rat.** Hazleton UK, Project ID TOX 86156. DPR Document 287-064 #65359.

McIntyre, M., 1987b. **T279 Technical Amitraz: Teratogenicity study in the rabbit.** Hazleton UK, Project ID TOX 86157. DPR Document 287-064 #65362.

Mehler, L., S. Edmiston, D. Richmond, M. O'Malley, and R. Krieger, 1990. **Summary of Illness and Injuries Reported by California Physicians as Potentially Related to Pesticides 1988.** HS-1541, April 1990.

Mehler, L., 1991. **Summary of Illness and Injuries Reported by California Physicians as Potentially Related to Pesticides 1989.** HS-1624, August 1991.

Meister, R.T., Editor in Chief, 1994. **Farm Chemicals Handbook '94.** Meister Publishing Company, Willoughby, Ohio.

Merryman, D.C., and M.M. Sutton, 1972. **BTS 27 419 Effects on the Oestrus Cycle of the Rat**. Monthly Report - February 1972, The UpJohn Company. DPR Document 287-008 #984644.

Metcalf, W., 1972. **BTS 27 419: Formulations SN 6323 and SN 6554 Irritancy to Rabbit Skin**. The UpJohn Company. DPR Document 287-012 #984490.

Morgan, H.E., D.S.G. Patton and G.J. Turnbull, 1983. **BTS 27 419: Two-Year Oral Toxicity Study In Dogs**. DPR Document 287-012 #984555.

Moriya, M., T. Ohta, K. Watanabe, T. Miiyazawa, K. Kato, and Y. Shirasu, 1983. **Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems.** DPR Document 287-042 #1116.

Moser, V.C. and R.C. MacPhail, 1989. **Investigation of Amitraz neurotoxicity in rats, III. Effects on motor activity and inhibition of monoamine oxidase**. Fundamental and Applied Toxicology, 12:12-22.

Needham, D. and P.A. Hemmings, 1988. **The metabolism and distribution of Amitraz® residues in the laying hen following the daily oral administration of 24.5 mg (^{14}C)-Amitraz per bird for 4 days**. NOR-AM Company study M75. DPR Document 287-071 #73432.

Oshita, C.M., F.A. Schneider, and S. Margetich, 1986. **An exposure study of mixer/loaders and applicators using oxydemeton-methyl (Meta-Systox R^{0})in Salinas and Santa Maria Valleys of California in 1986.** DPR, WH&S Branch HS Report-1398.

Palmer, A.K., and P.A. James, 1977a. **Dominant Lethal Assay of Amitraz in the Female Mouse.** Huningdon Research Centre, Huntingdon, Cambridgeshire, BFC Chemicals, Inc. DPR Document 287-054 #51319.

Palmer, A.K., and P.A. James, 1977b. **Dominant Lethal Assay of Amitraz in the Male Mouse.** Huningdon Research Centre, Huntingdon, Cambridgeshire, BFC Chemicals, Inc. DPR Document 287-054 #51320.

Patton, D.S.G., 1973. **BTS 27-419: Acute Toxicity in Baboons**. Submitted by The UpJohn Company in application for pesticide registration. DPR DOCUMENT 287-008 #984450.

Patton, D.S.G., and M.M. Sutton, 1971. **Acute Toxicity Studies on BTS 27-419 an acaricide (oral toxicities in the mouse, rat, guinea pig, rabbit, and dogs; dermal toxicity in the rat)**. The UpJohn Company. DPR DOCUMENT 287-008 #984436.

Patton, D.S.G., and G.A.H. Williams, 1973. **BTS 27-419: 90-Day Toxicity Study in Dogs**. Submitted by The UpJohn Company in application for pesticide registration. DPR DOCUMENT 287-009 #984541.

Paul, P.F. and J.J. Vukich, 1994. **AMITRAZ®: Evaluation of data supporting the safety of Mitac WP and Mitac EC applied to pears for control of pear psylla and to support the reregistration of Amitraz**. AgroEvo USA Company study. DPR Document 287-107 #132500.

Petzold, G.L., J.A. Swenberg, and M. Bedell, 1977. **Evaluation of Amitraz (U-36,059) and Its Metabolites (U-40,481, U-36,893, U-54,915A, and U-54,914) in the DNA Damage/Alkaline Elution Assay**. Nor-Am Chemical Company, Code Number 7263/77/7263/008. DPR DOCUMENT 287-074 #75275.

Seaman, W.J., and P.K. Brown, 1979a. **Acute oral LD_{50} in rats with BAAM® 50W**. The UpJohn Company. DPR Document 287-033 #984423.

Seaman, W.J., and P.K. Brown, 1979b. **Dermal Irritation and dermal LD_{50} with BAAM® 50W formulation in New Zealand rabbits**. The UpJohn Company. DPR Document 287-033 #98481.

Seaman, W.J., and P.K. Brown, 1979c. **BAAM® 50W- Primary eye irritation evaluation in New Zealand white rabbits**. The UpJohn Company. DPR Document 287-033 #984507.

Sharp, D.W., and P.C. Saunders, 1983. **The acute dermal toxicity of TAKTIC® EC formulation CR-15875 to the rat**. FBC Ltd. DPR Document 287-060 #64174.

Sharp, D.W., and P.C. Saunders, 1984. **The acute oral toxicity of TAKTIC® EC formulation CR-15875 to the rat**. FBC Ltd. DPR Document 287-060 #64173.

Shaw, J.W., 1973a. **BTS 27-419: Acute Oral Toxicity to Male and Female Rats**. The UpJohn Company. DPR DOCUMENT 287-008 #984446.

Shaw, J.W., 1973b. **BTS 27-419: Comparison of the acute oral and intraperitoneal toxicities to rats**. The UpJohn Company. DPR DOCUMENT 287-008 #984440.

Shaw, J.W., and G.A.H. Williams, 1971. **BTS 27-419: 90-Day Chronic Study in Mice**. Submitted by the UpJohn Company in support of product registration. DPR Document 287-009 #984539.

Shaw, J.W., and G.A.H. Williams, 1975. **BTS 27-419: Acute Oral Toxicity to Rats of 20% Emulsifiable Concentrate Formulation SN 6554**. Submitted by the UpJohn Company in support of product registration. DPR Document 287-008 #984454.

Shirley, D.B., 1975. **Analysis of tissue from pigs treated with Amitraz at Thurgarteon Research Station**. FBC Ltd. DPR Document 287-061 #63320

Shirley, D.B., 1977. **Amitraz residues in cattle from Wiltonside Total Replenishment Tank, South Africa**. FBC Ltd. DPR Document 287-061 #63319

Snowdon, P.J., 1982. **Tissue residue study following dermal spray application of Amitraz (formulation TAKTIC®) to beef cattle in the USA**. FBC Ltd. DPR Document 287-061 #64178.

Stewart, F.P., 1993. **^{14}C-amitraz: dermal absorption in the rat**. DPR Document 287-104 #.

Somerville, D., and J.E. Nicholson, 1976. **Leaching of Amitraz in Soil**. UpJohn Company. DPR Document 287-006 #984309.

Sumerville, D., 1973. **BTS-27,419 (Amitraz) soil degradation studies - a preliminary report**. LEACHING of Amitraz in soil. The UpJohn Company. DPR DOCUMENT 287-006 #984301.

Sumerville, D., and J.E. Nicholson, 1976. **Leaching of Amitraz in soil**. The UpJohn Company. DPR DOCUMENT 287-006 #984309.

Sumerville, D., J.E. Nicholson, and J.E. Taylor, 1975. **Amitraz (BTS-27,419): Degradation studies in an American sandy loam soil**. The UpJohn Company. DPR DOCUMENT 287-006 #984305,7.

Sutton, M.M., 1970. **Comparison of acute toxicities to rats of RD 27-271, 27-419 (Amitraz and 21-103**. The UpJohn Company. DPR DOCUMENT 287-008 #984434.

Sutton, M.M., 1971. **BTS-419 Contact Sensitization in the guinea pig**. The UpJohn Company. DPR DOCUMENT 287-012 #984527.

Sutton, M.M., 1973a. **BTS 27-419: Three Week Dermal Toxicity to Rabbits**. Conducting laboratory not indicated, data submitted as part of an application for new pesticide product registration by the UpJohn Company. DPR DOCUMENT 287-012 #47249.

Sutton, M.M., 1973b. **BTS 27-419: Multigeneration Feeding Test in Rats**. The Boots Company Ltd. DPR DOCUMENT 287-048 #36385.

Sutton, M.M., 1973c. **BTS 27-419: Teratogenicity in the Rat**. The Boots Company Ltd. DPR DOCUMENT 287-048 #36383.

Sutton, M.M., 1973d. **BTS 27-419: Effect on Pregnancy, Parturition and Care of the Young in Rats**. The Boots Company Ltd. DPR DOCUMENT 287-012 #984569.

Sutton, M.M., 1973e. **BTS 27-419: Teratogenicity in the Rabbit**. The Boots Company Ltd. DPR DOCUMENT 287-048 #036388.

Sutton, M.M., and W. Metcalf, 1972. **BTS 27-419 Eye irritancy in the rabbit**. The Boots Company Ltd. DPR DOCUMENT 287-012 #984511.

Sutton, M.M., and J. Offer, 1973. **BTS 27-419: Carcinogenicity and Long-Term Toxicity Study in Rats**. The Boots Company Ltd. DPR DOCUMENT 287-049 #36396.

Sutton, M.M., and G.A.H. Williams, 1971. **BTS 27-419: 90-Day Toxicity Study in Rats**. The Boots Company Ltd. DPR Document 287-054 #51309.

TAS, 1992a. Exposure-4™. **Detailed Distributional Dietary Exposure Analysis**, Version 3.2. Technical Assessment Systems, Inc., Washington, D.C.

TAS, 1992b. Exposure-1™. **Chronic Dietary Exposure Analysis**, Version 3.2. Technical Assessment Systems, Inc., Washington, D.C.

Thomas, B., 1984. **Amitraz: A Toxicological Overview**. Submitted with new data on amitraz in fupport of registrations of MITAC, BAAM, and TAKTIC, Nor-Am Chemical Company and the Upjohn Company. DPR DOCUMENT 287-041.

Toyoshima, S., and H. Fujita, 1972a. **Three Month Feeding Study on Rats**. Japan Experimental Medical Research Co. DPR Document 287-009 #984535.

Toyoshima, S., and H. Fujita, 1972b. **Three Month Feeding Study on Mice**. Japan Experimental Medical Research Co. DPR Document 287-009 #984537.

UpJohn Company, 1976. **Application for new pesticide product registration BAAM® EC miticide/insecticide for apples and pears**. Book III, Residue chemistry. DPR DOCUMENT 287-005.

UpJohn Company, 1981. **Application for new pesticide product registration BAAM® WP**. DPR DOCUMENT 287-033.

USDA (United States Department of Agriculture), 1988. **Data set: NFCS 87-I-1 Nationwide Food Consumption Survey.** 1987-88. Preliminary report unpublished.

U.S. EPA (United States Environmental Protection Agency), 1983. **List of Chemicals Evaluated for Carcinogenic Potential**. Memorandum from Reto Engler, Senior Science Advisor, Health Effects Division/OPP, Environmental Protection Agency, August 31, 1993.

U.S. EPA (United States Environmental Protection Agency), 1985. **Toxicology to EPA Registration Standard For Amitraz**. DPR Document 287-050.

U.S. EPA (United States Environmental Protection Agency), 1987a. **Guidance for the Reregistration of Pesticide Products Containing Amitraz as the Active Ingredient**. Office of Pesticide Programs, Washington DC.

U.S. EPA (United States Environmental Protection Agency), 1987b. **Fact Sheet #147 Office of Pesticides and Toxic Substances**, Office of Pesticide Programs, Washington, D.C., Oct. 1987.

U.S. EPA (United States Environmental Protection Agency), 1987c. **Reference Dose (RfD): Description and Use in Health Risk Assessments.** Integrated Risk Information System (IRIS), Appendix A. Intra-Agency Reference Dose Work Group, U.S. EPA, Environmental Criteria and Assessment Office, Cincinnati OH.

U.S. EPA (United States Environmental Protection Agency), 1988. **Amitraz; establishment of temporary tolerances**. Federal Register, 40 CFR Part 180 Vol 53, No. 169, 8-31-88, p33536-37, Washington, D.C.

U.S. EPA (United States Environmental Protection Agency), 1993. **Amitraz; Tolerances for Residues**. Code of federal regulations (CFR) 40 Parts 150 to 189, revised as of July 1, 1993, 180.287, p380, Washington, D.C.

U.S. EPA (United States Environmental Protection Agency), 1994. **List of Chemicals Evaluated for Carcinogenic Potential.** Memorandum from Reto Engler, Senior Science Advisor, Health Effects Division/OPP, Environmental Protection Agency, April 1, 1994.

Vukich, J.J., 1993. **Amitraz Containing Formulations CR 16013, CR 15773, and OVASYN 15773, and OVASYN (CR 18990): Composition and Data on Inert Ingredients.** Material Safety Data Sheet as of 1/31/92. DPR Document 287-100 #125452.

Ware, G.W., 1978. **The Pesticide Book**, W.H. Freeman and Co., pp 197.

Weddon, T.E., and M.M. Gargano, 1975a. **U-36059 Dermal LD_{50} and irritation evaluation in rabbits with BAAM® EC formulation containing 1% propylene oxide**. The UpJohn company. DPR Document 287-012 # 984492.

Weddon, T.E., and M.M. Gargano, 1975b. **U-36059 Dermal irritation/sensitization evaluation in the guinea pig with a BAAM® EC formulation containing 1% propylene oxide**. The UpJohn company. DPR Document 287-012 # 984451.

Weddon, T.E., and M.M. Gargano, 1975c. **Eye irritation study in rabbits with BAAM® EC formulation containing 21.4% U-36059 and 1% propylene oxide**. The UpJohn company. DPR Document 287-012 # 984514.

Weddon, T.E., and M.M. Gargano, 1975d. **U-36059 Acute oral LD_{50} in rats with a BAAM® 50W formulation**. The UpJohn company. DPR Document 287-033 # 984424.

Weddon, T.E., and M.M. Gargano, 1975e. **U-36059 Dermal LD_{50} and skin irritation evaluation in rabbits with a BAAM® 50W formulation**. The UpJohn company. DPR Document 287-033 # 984484.

Weddon, T.E., and M.M. Gargano, 1975f. **Eye irritation evaluation in New Zealand white rabbits with a BAAM® 50W formulation**. The UpJohn company. DPR Document 287-033 # 984506.

Weddon, T.E., and M.M. Gargano, 1976a. **U-36059 One hour inhalation toxicity in rats of a BAAM® EC formulation containing 1% propylene oxide**. The UpJohn company. DPR Document 287-012 # 984503.

Weddon, T.E., and M.M. Gargano, 1976b. **U-36059 One hour inhalation toxicity in rats with a BAAM® 50W formulation containing 1% propylene oxide**. The UpJohn company. DPR Document 287-033 #984500.

Whiting, K.G., 1979. **The Stability of Amitraz to Hydrolysis and Light**. BFC Chemicals Inc. DPR Document 287-055 #52908.

Wilcox P., 1976. **BTS 27 419: Mutagenicity Study in the Intraperitoneal Host-Mediated Assay**. UpJohn and Boots. DPR Document 287-074 #75227

Zimmer, D.M., J.H. Mazurek, and B.K. Bhuyan, 1977. **T93-Evaluation of Amitraz (U-36,059 and Its Metabolites in the Salmonella Microsome Test**. FBC Limited, Chesterford Park Research Station, Essex, England. UpJohn & Boots Report 7268/77/7268/002. DPR Document 287-074 #75274.

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

By

David Haskell, Associate Environmental Research Scientist
HS-1529
June 29, 1989, revised June 2, 1993,
September 15, 1993, November 14, 1994,
December 12, 1995

California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch
1020 N Street, P.O. Box 94271
Sacramento, California 94271-0001

ABSTRACT

Amitraz is the common name for N'-methyl-N'-2,4-xylyl-N(N-2,4-xylylformimidoyl) formamidine, a miticide and insecticide registered for use on cotton, livestock, pears and in pet collars. EPA has classified amitraz as a quantifiable Group C/D carcinogen for which no clear evidence of oncogenic potential has been demonstrated. Studies submitted in response to the Birth Defects Prevention Act (SB 950) indicate that exposure to amitraz may cause adverse health effects (tumors and reproductive toxicity). A dermal absorption study in rats observed that with a 10 hour exposure, 13.8% of a 10 μg/cm^2 dose was eventually absorbed and excreted in 120 hours with minute amounts remaining in the carcass and gastrointestinal tract. Orally administered amitraz in rats is rapidly hydrolyzed in the stomach and eventually excreted in the urine as 4-acetamido-3-methyl benzoic acid (FBC-31158), 4-formamido-3-methyl benzoic acid (BTS-39098) and the highly polar conjugates of FBC-31158, BTS-39098, N-(2,4-dimethylphenol)-N-methyl formamidine (BTS-27271) and 4-amino-3-methylbenzoic acid (BTS-28369). A biomonitoring study for operators mixing, loading and applying amitraz in a pear orchard observed the excretion of amitraz metabolites in urine averaged 0.51 mg during the 120 hour collection period. Workers involved in the aerial application of amitraz to cotton may incur 3.51-11.4 mg of dermal exposure per day during mixing/loading, application or flagging. The maximum dermal exposure to workers making treatments to livestock was estimated to be 2.42 mg/day for a large cow-calf ranch. Harvesters picking in an pear orchard treated 7 days previously with amitraz could experience 20.3 mg of dermal exposure per 8-hour workday. The estimated absorbed daily dose for a veterinarian placing amitraz collars on dogs was 0.05 μg/kg.

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

Human Exposure Assessment

AMITRAZ

December 12, 1995

GENERAL PHYSICAL AND CHEMICAL PROPERTIES

Amitraz is the common name for N-methyl-N'-2,4-xylyl-N(N-2,4- xylylformimidoyl) formamidine, a miticide and insecticide sold under the trade names "Mitac®" and "Taktic®" by the Nor-Am Company (Upjohn Company, 1976). It is a pale, straw colored crystalline solid with a melting point of 86-87^{o}C. Amitraz has a specific gravity of 0.905 at 20^{o}C and a boiling point of 140^{o}C. The vapor pressure of amitraz has been determined by an effusion method to be 3.8 X 10^{-7} mm mercury at 20^{o}C. Amitraz is poorly soluble in water (less than 1 ppm at 22^{o}C), but is readily soluble in most organic solvents (1 gm dissolving in 1.5 ml of xylene). This compound is relatively stable to heating in the dry form or when immersed in an organic solvent but becomes increasingly unstable in water as the pH drops. In an aqueous solution with a pH of 6.18, the half-life is 172 minutes at room temperature. However, when the pH is lowered to 4.13, the half-life is only 15.3 minutes.

The technical material has a minimal purity of 93% with 2.5% paraformaldehyde added to prevent oxidation (Upjohn Company, 1976). During formulation most of the paraformaldehyde is removed because of its low solubility in the formulating solvents. Only 0.02-0.07% of the formulated product is paraformaldehyde. The primary impurities in the technical material are N,N'- di-(2,4-dimethylphenyl) formansidine (6% or less) and 2,4-xylidine (0.3% or less).

EPA STATUS

The manufacturer of amitraz applied for a registration on apples and pears in 1976. In April 1977, before registration could be completed, the Environmental Protection Agency (EPA) issued a Rebuttable Presumption Against Registration (RPAR) document for amitraz (U.S. EPA, 1979). Based on an 80-week mouse oncogenicity study, the Agency concluded there is "weakly positive evidence" that amitraz is a possible human carcinogen.

In October 1979, the RPAR was concluded with the recommendation that a four-year conditional registration was justified on pears, but not on apples. Amitraz became a federally restricted material with a 24-hour reentry interval and a seven-day pre-harvest interval. Labeling was

amended to require protective clothing to be worn by the mixer/loader and applicator. The Agency determined that the continued registration of amitraz on pears would not pose any unreasonable risks and granted a four year conditional registration in January 1980.

In October 1987, the guidance document for the reregistration of amitraz was issued (U.S. EPA, 1987a). The EPA's Cancer Assessment Group (CAG) has completed their evaluation of the new mouse oncogenicity study. The initial CAG review, based on the weight of evidence, indicated that amitraz should be considered as a possible human carcinogen in the lower portion of the group "C" range. Their conclusions were reviewed by the FIFRA Scientific Advisory Panel (SAP) along with additional opinions from the manufacturer of amitraz. The SAP concluded that amitraz should be classified in group D (not classifiable as to human carcinogenicity). EPA has since reassessed its own position in light of the industry presentation and the SAP opinion. The Agency has now concluded that amitraz is a group C/D carcinogen in regard to it's oncogenic potential. As a result, amitraz will no longer be required by the EPA to be registered as a restricted use pesticide.

In the guidance document, the Agency also listed the conditions necessary to reregister manufacturing-use and end-use products. The makers of manufacturing-use products must conduct additional environmental fate, avian reproduction and metabolism studies to maintain registration.

USAGE

The annual Pesticide Use Reports compiled by the Department of Pesticide Regulation (DPR) indicate that 5,834 lbs. of active ingredient (a.i.) were used to treat 4,126 acres of pears in 1991 (DPR, 1993). In 1992, 8,952 lbs. of a.i. were used to treat 6, 327 acres of pears (DPR, 1994). Although amitraz is now registered for use on cotton under the trade name Ovasyn®, the use report from the 1993 season indicates only 16 lbs. of a.i. was applied (DPR, 1995). Since livestock are not considered an agricultural commodity in California for the purposes of reporting pesticide use, dairymen, ranchers and feedlot operators are not required to report use to the Agricultural Commissioner. As a consequence, data regarding the annual amount of amitraz applied to livestock is not available.

FORMULATIONS

The Nor-Am Company has registered two formulations of amitraz for use on pears (Mitac® WP and Mitac® EC), a third formulation for use on cotton (Ovasyn®) and a fourth formulation for use on livestock (Taktic®). Mitac® WP (wettable powder) is composed of 50% active ingredient formulated with earth-derived carriers, a surfactant and a dispersing agent. The label allows a maximum application rate of three lbs. of product per acre with a maximum seasonal use of three lbs. of a.i. The pre-harvest interval is seven days. Mitac® EC and Ovasyn® are emulsifiable concentrates formulated with 1.5 lbs. of active ingredient per gallon. A petroleum distillate

blended with an emulsifier make up the remaining percentage (80%) of inerts. Mitac® EC permits 2-4 quarts of product per acre on pears to be applied with a seven-day pre-harvest interval. The maximum seasonal use is three lbs. of a.i. per acre. Ovasyn® permits a label rate of 0.125-0.94 lb. a.i. per acre per application on cotton with a maximum seasonal use of 1.0 lb. a.i. per acre. Taktic® is registered as a miticide/insecticide to control ticks, mange mites and lice on livestock. Taktic® is formulated as a 12.5% (by weight) emulsifiable concentrate with 0.94 lb. of amitraz per gallon. Applications to beef and dairy cattle are made as a mixture of one-two cans (25.7 oz. each) per hundred gallons of water (0.4-0.8% solution by weight). Each animal can be treated with a maximum of two gallons of spray mixture. Swine and their pens are treated with a mixture of one can of product per 50 gallons of water (0.8% solution by weight) to control body lice. The adult pigs are treated with a coarse spray until run off while piglets or weaners can be dipped in the mixture. One manufacturer of pest control products for dogs has registered a pet collar for dogs impregnated with amitraz to control ticks.

LABEL PRECAUTIONS

The protective clothing required for handling products that contain amitraz vary according to the toxicity of the formulation. The pet collar label recommends the handler to wash thoroughly with soap and water after handling the collar. Taktic®, a category III pesticide, requires persons handling it to wear long pants, long-sleeved shirt, chemical resistant gloves, a hat, socks, boots and protective eyewear. Workers mixing and loading Taktic® must also wear a chemical resistant apron. Mitac® EC and WP are category II pesticides that require coveralls to be worn over long-sleeved shirt and long pants, waterproof or chemical resistant gloves, chemical resistant footwear plus socks, chemical resistant headgear, and protective eyewear. In addition workers mixing/loading or cleaning application equipment must wear a chemical resistant apron. The Ovasyn® label requires the same protective clothing to be worn as listed on the Mitac® EC and WP labels. In addition, as a category I liquid pesticide, California regulations require Ovasyn® to be mixed and loaded with a closed system when handled by employees. Under the federal “Worker Protection Standards”, when a "closed system" is used to mix and load a pesticide with the signal word DANGER or WARNING, workers can wear long-sleeved shirt and long pants, shoes and socks, chemical resistant gloves, chemical resistant apron and protective eyewear (if the closed system is pressurized). This protective clothing regime is consistent with the California regulations for protective clothing when a "closed system " is used. The label prohibits entry into treated areas for 24 hours after the application unless the appropriate protective clothing is worn. Workers entering treated areas after the 24-hour period has elapsed can wear normal work clothing. The Ovasyn® label and the labels for Mitac® EC and WP caution the handler that repeated skin contact may cause an allergic reaction.

WORKER ILLNESSES

The DPR, Worker Health and Safety Branch (WH&S) has not received any reports of worker illnesses due to exposure to amitraz from 1984-1993, the last year for which published reports

are available (CDFA, 1985; CDFA, 1986; CDFA, 1987; Edmiston and Richmond, 1988; Mehler *et al.*, 1990; Mehler, 1991; DPR, 1993a; DPR, 1994a; DPR, 1994b; DPR, 1995a).

DERMAL TOXICITY

The effects of dermal exposure to amitraz have been well studied. Dermal irritation studies were conducted on rabbits with the formulated EC and WP products applied as a single dose (up to 2000 mg/kg) or as multiple doses (500 ppm) (BFC Chemicals, 1981). Systemic effects of hypothermia, hyperglycemia and depression were reported but subsided after 48 hours. The dermal dose of 2,000 mg/kg did not attain the LD_{50} for amitraz. This dose did incite a mild irritation producing slight erythema and edema after 24 hours that was reversed by 72 hours. The EC formulation produced moderate dermal irritation, which was attributed to the petroleum solvent (BFC Chemicals, 1981).

Twenty-four male and female dogs were exposed to a single dose of 250, 1250, or 2500 ppm amitraz, equivalent to 16, 68 and 136 mg/kg of body weight applied over the whole body (Kakuk and Weddon, 1976). The animals were observed seven days post-treatment for clinical signs of toxicity. Dose related effects of sedation and hypothermia culminated within eight hours of the treatment. Blood glucose levels were slightly to moderately elevated in all dosage groups four hours post-treatment. All effects were transitory and returned to normal ranges within 24 hours of the treatment.

A human patch test with multiple 0.5-ml doses of the EC product applied per cm^2 of skin produced moderate irritation (BFC Chemicals, 1981). However, repeated exposures did not significantly alter the irritation intensity, which was probably due to the petroleum solvent.

DERMAL ABSORPTION

A dermal absorption study of ^{14}C labeled amitraz in rats was conducted by Hazelton Europe in compliance with US Good Laboratory Practice standards and the UK Principles of Good Laboratory Practice (Stewart, 1993). Adult male rats were obtained from the Charles River (UK) Ltd. colony and acclimatized for about one week. One to two days prior to the study, an area of the dorso-lumbar skin was shaved and washed with acetone. A silicone ring was attached to the shaved area that provided approximately 10 cm^2 of skin surface available for exposure. The nominal doses were administered in a suspension of amitraz formulation and deionized water at 0.1, 1.0 or 10 mg of amitraz per animal equivalent to 10, 100, and 1,000 ug/cm^2. The treatment sites were protected with nonocclusive covers. After dosing, the rats were placed in individual all-glass metabolism cages suitable for the separate collection of the urine and feces. Four animals were used per sacrifice time per dose. Daily urine and feces samples were collected and analyzed separately. The animals in each dose group were exposed to their doses for 0.5, one, two, four or ten hours. After the exposure period the rats were sacrificed with the exception of the rats exposed for ten hours. These animals had their dose removed by swabbing with detergent soaked swabs and they were kept alive an additional 14 or 110 hours. The samples

collected for analyses were: nonocclusive covers, back washings, treated skin sites, cage washings/debris, blood, carcasses, feces, and urine.

Total recovery of the applied radioactivity ranged from 85-124% for all animals with the majority of the radioactivity (81-117%) recovered from the dose dressing and the wash-off solution. The highest percentage of the dose present at the application site after wash-off was 12.1 % at the four-hour sacrifice for the low dose animals. The percent of the dose present at the treated skin sites after wash-off for the medium and high doses was also highest four hours after administering the dose. Table I lists the results from analysis of the urine and feces samples collected following the 10 hour exposure period for the three dosage groups. The absorbed amitraz was excreted primarily in the urine with the rate of excretion decreasing with time. For all dose groups, the rate of excretion of the radiolabel in the urine and feces appears to plateau at about five days. The results indicate the dermal absorption rate of amitraz is dose dependent. A greater percentage of the low dermal dose (10 ug/cm^2) is excreted in the urine and feces than the 100 and 1,000 ug/cm^2 doses.

To calculate a rate of dermal absorption, the values from Table I for the 10-hour exposure period and the 120-hour sacrifice time were used. The cumulative value for the percentage of the dose detected in the urine and feces after 120 hours was corrected for the residues of amitraz that may still be present at the skin application site and is bioavailable. This correction was derived by employing an exponential saturation model with lag time to estimate the asymptote for the curve of the accumulative dose excreted versus time. An equation representing this model is: Y = A*(1-EXP(-B*(X+C))) or Recov = Max*(1-EXP(-Rate*(Time + Lag))). An example of the plots for the low dose and the outputs are shown in Figure 1. The corrected cumulative excretion in the urine and feces in conjunction with the amitraz detected in the blood, carcass, cage wash was used to estimate the rates of dermal absorption in Table II. These values were then corrected for the average percent recovery of the radioactivity for the appropriate dose group and sacrifice time to derive the final estimate of the dermal absorption rates.

Since the rate of dermal absorption for amitraz is dose dependent, the rate used to calculate the absorbed daily dose from an occupational exposure should be derived from a dose that is representative of the occupational exposure. The dermal exposures observed in the orchard air-blast exposure study (Castro and Ramos, 1988) averaged 3.8 ug/cm^2 for the hands and 4.7 ug/cm^2 for the body regions excluding the head and neck. In the surrogate exposure study used to estimate the exposure for aerial applicators (Maddy *et al.*, 1979), the dermal exposure ranged from 0.16 ug/cm^2 for the pilots to 0.54 ug/cm^2 for the mixer/loaders. The occupational exposure from applications of Taktic® to livestock was estimated from a study of cyromazine applications in a poultry house (Haskell *et al.*, 1993). The rate of exposure to the workers was dependent on the type of application equipment used with backpack sprayers experiencing the highest exposure rates at 0.88 ug/cm^2. In recognition of these observed and estimated rates of occupational dermal exposure, the 13.8% value derived from the rats dosed at 10 ug/cm^2 is the appropriate dermal absorption rate.

Table I. Percent dose of amitraz excreted following 10-hour exposure.

A. 0.1 mg/animal (10 ug/cm^2)

	Percent dose (mean)				
Time (h)	Urine (U)	Feces (F)	U + F		Cumulative
10	1.347	0.066	1.413		1.41
24	3.157	0.541	3.698		5.11
48	2.006	0.586	2.592		7.70
72	1.331	0.602	1.933		9.64
96	0.551	0.294	0.845		10.48
120	0.297	0.214	0.511		10.99
Total	8.689	2.303	10.992		

B. 1 mg/animal (100 ug/cm^2)

	Percent dose (mean)				
Time (h)	Urine (U)	Feces (F)	U + F		Cumulative
10	0.572	0.061	0.633		0.63
24	1.487	0.097	1.584		2.22
48	1.564	0.307	1.871		4.09
72	0.623	0.357	0.98		5.07
96	0.313	0.188	0.501		5.57
120	0.154	0.081	0.235		5.80
Total	4.713	1.091	5.804		

C. 10 mg/animal (1000 ug/cm^2)

	Percent dose (mean)				
Time (h)	Urine (U)	Feces (F)	U + F		Cumulative
10	0.115	0.021	0.136		0.14
24	0.681	0.267	0.948		1.08
48	0.771	0.341	1.112		2.20
72	0.479	0.21	0.689		2.89
96	0.257	0.137	0.394		3.28
120	0.191	0.153	0.344		3.62
Total	2.494	1.129	3.623		

Table II. Summary: Dermal absorption of amitraz in male rats*a.

Dose	Percent dose (mean)*b						
(ug/cm^2)	Excreted*c	Blood	Carcass	Cage wash	Sub-total	Recovery(%)	Total abs.*d
10	11.36	0.02	0.24	1.41	13.03	94.2	13.83
100	6.17	0.02	0	0.74	6.93	104.4	6.64
1000	4.06	0.01	0.8	0.52	5.39	95.1	5.67

*a Based on 10-hour exposure time and 120-hour sacrifice time.

*b Percent doses: excreted + blood + carcass + cage washings/debris.

*c At asymptote using an exponential saturation model.

*d Adjusted to reflect 100% recovery.

The results from the Hazelton Europe Laboratory dermal absorption study are supported by a similar study conducted by Challis (1990) with one dosage rate. In this study, rats were dosed at one mg per animal, equivalent to 91 ug/cm^2, with an aqueous dosing solution of ^{14}C-labeled amitraz suspended in the Mitac® formulation. After ten hours the dose was removed with tissue paper moistened with soap and water. Urine and feces were collected at 24-hour intervals after the start of the treatment. At 24 hours after treatment, five animals were sacrificed and the remaining five were maintained in metabolism cages for five days and then sacrificed. At sacrifice, the excreta, tissues, application site apparatus and dressings, application site skin, and the carcass with the gastrointestinal tract were analyzed for radioactivity. An additional two rats were given a single oral dose of 0.1 mg of amitraz in corn oil and maintained for 24 hours during which their urine was collected for analysis.

The percent of the dose detected in the excreta, cage wash, carcass and gastrointestinal tract was considered absorbed. A 6.6% dermal absorption rate was derived as the sum of the percentage excreted after 120 hours and the percentage detected in the gastrointestinal tract and carcass at sacrifice. Since the curve derived from plotting the accumulative excretion (urine and feces) over the five-day period approaches the maximum level of excretion, the 1.4% of the dose bound to the application site was not considered bioavailable.

An earlier study conducted by the FBC Limited Laboratory (Essex, England) in 1984, involved the treatment of pigs with ^{14}C-labeled amitraz (Campbell and Needham, 1984a) was reviewed. However, some of the parameters and the results of the pig study limit its value for use in estimating the rate of dermal absorption of amitraz in humans. Since only four animals were used in the study, the sample size may not be large enough to be representative. The dosage rate of 180 ug/cm^2 is two orders of magnitude greater than the exposure rates estimated in the worker exposure studies through biomonitoring. Almost 30% of the dose remained bound to the skin after wash-off. Without adequate excretion data, this percentage of the dose would be assumed to be absorbed following the Procedure for Studying Dermal Absorption (U.S. EPA, 1987b). The range of total recoveries (74-95%) for the animals indicates there may have been some problems with the analytical methodology.

ANIMAL METABOLISM

The metabolic fate of amitraz has been studied in several different test species at the FBC Limited Laboratory in England (Hornish and Nappier, 1983), (Campbell, 1984a). Although details of the recoveries from the spiked samples were not described, the total recovery from the urine and feces samples averaged better than 90 percent. The theoretical metabolic pathways are outlined in the metabolic flow diagram located after the references.

Administered as an oral dose, ^{14}C-labeled amitraz is rapidly excreted, primarily in the urine. The following percentages (means) of the dose were excreted in urine 24 hours after administration: dog-48.4%, mouse-57.6%, baboon-64.8% and rat-74.9%. These figures include the peak levels

of radioactivity in the urine. Peak levels in the blood of mice and dogs, following an oral dose, occurred within 1.5-6 hours.

Of the various species, the baboon accumulated the highest percentage of an oral dose in the tissues (Campbell, 1984b). The following concentrations of radioactive residues (mg equivalents per kg of fresh tissue) were detected 72 hours after a single dose at 10 mg/kg; liver (4.64-5.11 ppm), bile (2.17-2.93 ppm), whole eye (1.01-1.56 ppm), adrenal gland (0.25-0.72 ppm) and kidney (0.57-0.62 ppm). There were only minor differences in the excretion rates between the male and female of each species.

A mouse study compared the metabolic fate of ^{14}C-labeled amitraz fed to mice for three weeks versus those fed a normal diet (Campbell and Needham, 1983). All animals were then administered a single oral dose of 20 mg/kg of body weight of ^{14}C-labeled amitraz. The pre-exposure had little effect on the magnitude or distribution of the tissue residues. In both test groups, average residues were highest in the liver (0.5 ppm) and adrenal glands (0.45 ppm) and lowest in the bone (0.06 ppm) and muscle (0.04 ppm).

Two human male volunteers were given a single oral dose of 0.25 mg/kg of ^{14}C-labeled amitraz (Campbell and Needham, 1984b). Excretion in the urine was measured over a 72-hour period. Seventy-eight percent of the dose was excreted during the first 48 hours with 82% excreted during the test period. This excretion rate is comparable to those of the test animals.

A metabolic fate study was conducted on rats administered orally, one, 10, 50 and 100 mg/kg dosages of ^{14}C-labeled amitraz (Campbell and Needham, 1984c). Urine samples were collected for 24 hours after administering the doses and were used for identifying and quantifying the metabolites. The study focused on the excreted urine from the 100-mg/kg dosage. Results from the other dosages were used to characterize the identity and quantity of the metabolites at these dosages.

Essentially all of the dose was rapidly hydrolyzed in the stomach. In the urine, N-(2,4-dimethylphenyl)-N-methyl formamidine (BTS-27271), 2,4- dimethylformanilide (BTS-27919), 4-amino-3-methylbenzoic acid (BTS-28369), 4-formamido-3-methyl benzoic acid (BTS-39098), 4-acetamido-3-methyl benzoic acid (FBC-31158) and N-2,4-dicarboxyphenyl-N'-methyl formamidine (Metabolite A) were isolated by TLC and/or HPLC and confirmed by mass spectroscopy (Campbell, 1984a), (Campbell, 1984b). Traces of 2,4-dimethylaniline (BTS-24868) were evident by TLC in the urine, but they were too volatile to identify further.

At the 100 mg/kg dose level, each of these metabolites accounted for 1% or more of the radioactivity in the urine; BTS-27271 (23.0-29.0%), BTS-27919 (0.9-1.9%), BTS-28369 (0.3-1.2%), BTS-39098 (11.0-12.7%), FBC-31158 (16.5-19.1%) and the highly polar metabolites 40.2%. The highly polar fraction consisted of conjugates of BTS-28369, BTS-39098, FBC-31158, and BTS- 27271. These labile conjugates and the free BTS-39098 and FBC-31158 are converted to BTS-28369 by acid hydrolysis.

At all dose levels, BTS-39098 and FBC-31158 were major metabolites, accounting together for up to 31.8% of the excretion in urine. The excretion of BTS-27271 was dose dependent. At one mg/kg of body weight, only 4% of the dose was excreted as BTS-27271. BTS-24868 has been described as an intermediate metabolite that forms immediately after ingestion of an oral dose (Campbell and Needham, 1984c). Rats administered a 100 mg/kg oral dose excreted an average of 0.4% of the dose as BTS-24868 in the urine. When given a one and 10 mg/kg dose, the percent of BTS-24868 excreted in urine averaged one percent or less of the administered dose. BTS-24868 is then thought to breakdown to 4-amino-3 methylbenzoic acid in vivo.

The excretion of the metabolite BTS-27271 was found to be dose dependent in the tested animals (Campbell, 1984a). With an increase in the dose, the proportion of the urine that consisted of BTS-27271 also increased. The researchers theorized that amitraz is rapidly hydrolyzed to BTS-27271. BTS-27271 is then metabolized by an enzymatic process, which is easily saturated by high dosages. The excretion of amitraz metabolites in urine was investigated in rats, mice, baboons and humans (Campbell, 1984a). The spectrum of metabolites was qualitatively similar for all species tested and unaffected by sex or pre-exposure to amitraz. Mice, rats, and baboons were given a 10 mg/kg oral dose of ^{14}C-amitraz. The listed metabolites made up these percentages of radioactivity in the cumulative 24 hour urine sample; BTS-27919 [1.5% (rat)-1.9% (baboon)], BTS-28369 [1.9% (rat)-2.7% (baboon)], BTS-27271 [3.9% (rat)-5.4% (mouse)], BTS-39098 + FBC-31158 [17.2% (mouse)-26.5 (rat)], and polar material [53.4% (baboon)-61.8% (mouse)]. Humans were administered a 0.25 mg/kg oral dose and the urine was collected over a 96 hour period (Campbell, 1984a). These metabolites accounted for the following percentages of radioactivity in the urine; BTS-27919 (3.6%), BTS-28369 (3.8%), BTS-27271 (5.8%), BTS- 39098 + FBC-31158 (27.1%), and the polar materials (56.9%).

The EPA has concluded that 2,4-dimethylaniline (BTS-24868), one of the intermediate metabolites of amitraz, may pose an oncogenic risk to man (U. S. EPA, 1979). The results from a National Cancer Institute mice-feeding study were interpreted to exhibit a statistically significant increase in the incidence of pulmonary tumors. The EPA review of the Ames test results indicated a positive mutagenic response in one strain of bacteria had occurred (U. S. EPA, 1979). The Boots-Upjohn Company, owner of the amitraz product at that time, rebutted these EPA reviews.

Another study compared the metabolism of amitraz and BTS-27271 administered orally to white rats (Knowles and Benezet, 1981). Both amitraz and BTS-27271 were rapidly metabolized and eliminated primarily in the urine. In comparison to amitraz, a higher percentage of the BTS-27271 dose was eliminated in urine with an accompanying decrease in the feces. The degradation products of BTS-27271 detected in rat urine were similar to those found from metabolized amitraz.

The Upjohn Agricultural Research and Development Laboratories conducted an absorption and metabolism study on dogs dosed orally and dermally with ^{14}C-labeled amitraz (Hornish and Nappier, 1983). Oral absorption was rapid with nearly 80% of the dose excreted during the first 24 hours, primarily in the urine. The maximum blood levels from an oral four mg/kg dose were reached within eight hours post-treatment, ranging from 0.666-1.165 ppm (amitraz equivalents)

for five animals. Dermal absorption of a 20 mg/kg dose was much slower. Peak blood residue levels of 0.016-0.030 ppm (amitraz equivalents) were detected 24-168 hours post-treatment in four animals. After 9-11 days of exposure, 24-40% of the dermal dose had been excreted with the urine accounting for 75-89% of the excreted activity.

Whether administered as an oral or dermal dose, amitraz is metabolized essentially the same in dogs. The predominant metabolite in blood and urine is three-methyl-4 (N-formylamino)-benzoic acid (BTS-28369). The parent compound and the first-formed hydrolysis products were never observed at measurable levels in the blood and urine.

OCCUPATIONAL EXPOSURE

I. Orchard Air-Blast Operators

An orchard applicator exposure study was conducted by Hacker (1992) to measure the metabolites of absorbed amitraz that are excreted in urine and to quantify occupational exposure. Each operator (n = 7) was observed while mixing/loading and applying eight loads to pears with an air-blast sprayer at the maximum label rate of 1.5 lbs. a.i. per acre. The workers wore long pants and long-sleeved shirt underneath disposable coveralls, shoes or rubber boots, goggles and rubber gloves. Urine samples were collected for analysis 120 hours before the first exposure and for 120 hours after exposure to amitraz began. The urine samples were stored for an extended period of time (148-370 days) before analysis. The results from the extended storage stability studies were preliminary at the time of study submission and were not included. The rate of excretion of the metabolites in urine was determined by the conversion of the total urinary excretion (primarily FBC-31158, BTS-39098, and other conjugates) to BTS-28369 by acid hydrolysis and subsequent analysis for BTS-28369. A separate study in rats quantified this treatment to be 87% efficient in converting the total urinary excretion to BTS-28369 (Campbell and Needham, 1984c).

The urine analysis indicated the mean urinary excretion of amitraz metabolites for the workers applying Mitac® WP was 0.28 mg for the first 24 hours and 0.51 mg for the five-day period. Most of the operators excreted the largest portion of the metabolites during the first 24-hour interval after the start of the applications. To estimate what percentage of the absorbed dose of amitraz this value (0.51 mg) represents the human study by Campbell and Needham (1984b) was utilized. Eighty-two percent of a 0.25 mg/kg ^{14}C-labeled oral dose of amitraz was excreted as metabolites in the urine of two adult males over a 72-hour period. This excretion pattern is supported by observations made in animal exposure studies. In the pig, 6.7% of a dermally applied dose of ^{14}C-labeled amitraz was considered absorbed after 12 hours with 93% of the radioactivity associated with metabolites in the urine after a 60-hour excretion period (Campbell and Needham, 1984a). In the rat, 73% of the absorbed dermal dose was excreted as metabolites in the urine (Challis, 1990). The adequacy of the biomonitoring period (120 hours) for capturing the excretion of the absorbed dose is supported by the results from the same rat study. The accumulative excretion of the absorbed dose in urine and feces was considered 90% complete after 96 hours.

The identities of the metabolites in human urine and their relative percentages of the total excretion are similar to those identified in rats, mice and the baboon (Campbell 1984a). The polar fraction which comprised 60% of the excretion has been identified in rats to consist mainly of conjugates of FBC 31158, BTS-27271, BTS-39098 and BTS-28369 (Campbell and Needham, 1984b). The high percentage of the dose excreted in the urine and the observation that the parent compound was not detected in the urine indicates the oral dose was well absorbed and the metabolism is relatively complete. To correct for the percent of the radiolabeled dose that may have been excreted in the feces, lost during analysis or clean up or that remained in the tissues, the cumulative (5 days) urinary excretion from the biomonitoring study was divided by 0.82 (Campbell and Needham, 1984b).

In the exposure study by Castro and Ramos (1988), the operators mixed, loaded and applied an average of 14 loads per workday. The eight loads applied during the Hacker study represent 57% of the exposure the operator would be expected to receive during a full workday. To estimate the absorbed daily dose of amitraz from a full workday, the values in Table III were divided by 0.57.

Table III. Occupational Exposure to Amitraz for Operators in Pear Orchards

Operators[a]	Absorbed Daily Dosage (mg/workday)	Absorbed Daily Dosage[b] (ug/kg/day)	Annual Average Daily Dosage[c] (ug/kg/day)	Lifetime Average Daily Dosage[d] (ug/kg/day)
Mix/Load/Apply (N=7)				
mean (arith)	1.09	14.4	0.39	0.21
low	0.24	3.2	0.087	0.046
high	1.95	25.7	0.70	0.37

Haskell, WH&S, 1994·

[a] Operators mixed, loaded and applied 1.5 lbs. of active ingredient per acre with 400 gallons of water. The operators wore long-sleeved shirt and long pants underneath coveralls, goggles and rubber gloves.

[b] Calculated with a body weight of 76 kg for the worker.

[c] The staff of the Agricultural Commissioners offices for Lake and Sacramento Counties estimated 10 exposure days will occur annually.

[d] Calculated on the basis of a 75 year life span with 40 years of employment.

The results from the biomonitoring exposure study are supported by the observations made in a previous study of operators applying amitraz in a pear orchard. The Nor-Am Chemical Company completed a mixer/loader/applicator exposure study for Mitac® 50 WP in 1988 (Castro and Ramos, 1988). Mitac® 50 WP was applied with an air-blast orchard sprayer at the maximum recommended rate of 1.5 lbs. of a.i. per acre with 400 gallons of water. Typical for many orchard operations, one person performed the mixing, loading and application activities. Each operator wore at least the minimum protective clothing required by the label at that time; long-sleeve shirt, long pants, rubber gloves and boots. However, current Mitac® labels require workers to

wear the following additional protective clothing; coveralls over work clothing, protective eyewear, chemical resistant headgear and a chemical resistant apron during mixing and loading. Exposure was determined through passive dermal dosimetry (gauze patches) exposed directly to field conditions, hand washes, micro air pumps and urine testing.

The study was designed well and the results from the field study were presented in detail. Six operators mixed, loaded and sprayed 13 to 17 loads per day each, applying 19 to 25.5 pounds of active ingredient. Residues detected under the protective clothing averaged 82±36 mg (range 37-130). Exposure to the hands was minimal with a mean of 3.2±1.86 mg (range 0.23-5.12) detected. The mean inhalation exposure was 0.61±0.14 mg (range 0.48-0.84) for the 6 operators. These exposure rates probably represent an over estimation of the occupational exposure to amitraz because the current Mitac® label requires additional protective clothing to be worn by workers.

The results from the biological monitoring section of the mixer/loader/applicator exposure study are very similar to those observed in the Hacker (1992) study. The mean cumulative amount of amitraz equivalents detected in the human urine, 48 hours after the onset of the application exposure, was 0.39 mg. This figure, however, must be corrected for the percent recovery (76%) of the analyte BTS-28369 from the lab-fortified urine sample and then standardized for an 8-hour exposure period. The corrected value (0.61 mg) for the amitraz equivalents excreted in urine is within the range observed in the Hacker (1992) study.

Exposure studies utilizing patch dosimetry to observe dermal exposure have the tendency to overestimate exposure through the assumption that exposure is consistent within the body area represented by each patch. Many body regions (back, undersides of arms, back of legs) are partly protected from exposure by their orientation to the exposure activity. In conjunction with the exposure data, a rate of dermal absorption has to be estimated to calculate the absorbed dose. This rate is usually derived from an animal study with the assumption that the human rate is similar although human dermal absorption is typically much lower. Rates of clothing penetration may also have to be factored into the dermal exposure estimate. Because the metabolism of amitraz and the excretion of the metabolites are known quantitatively and qualitatively, the exposure data from the biomonitoring studies provided the most accurate determination of occupational exposure.

II. Field Crop Application

The Nor-Am Chemical Company has recently registered a new liquid formulation of amitraz, Ovasyn®, for use on cotton to control mites and other insect pests. Treatments can be made from the time the plants are 4-6 inches in height until the bolls start to open. Initially, the product was designated as a category II pesticide. However, since the current label is now designated as a category I pesticide, California regulations require Ovasyn® to be mixed and loaded with a closed system. Additional exposure data was not submitted to support this new use. The registration of amitraz on cotton represents a major new use that can incur exposure for handlers, flaggers and field checkers. Applications for early season mite and worm control (April-June) are expected to be made by growers with ground equipment (Goodell, 1993). Later in the season

(June-August), treatments for white flies and worms will be made by aircraft. Data from surrogate studies were used to estimate the occupational exposure from applications to cotton.

A. Ground Boom Application

A study of the occupational exposure incurred from applying oxydemeton-methyl (Meta-Systox R®) to vegetables was used as a surrogate study to estimate the exposure from applying Ovasyn® to cotton with a boom equipped tractor (Oshita *et al.*, 1988). The application rate, formulation type and type of application equipment were similar to applying Ovasyn® to cotton. Since oxydemeton-methyl has a much higher vapor pressure than amitraz, the observed inhalation exposure is expected to be much greater than for amitraz. The Meta-Systox R® formulation of oxydemeton-methyl was applied at a rate of 0.5 to 0.75 lb. a.i. per acre to cabbage, broccoli, cauliflower, and Brussels sprouts, using tractors equipped with boom sprayers or aircraft. Eleven workers were monitored for dermal and inhalation exposure during 24 workdays. Each worker wore a shirt, long pants, socks, and cloth coveralls. Additional protective clothing, consisting of chemical resistant gloves, boots, rainsuit or standard Tyvek® coveralls, hat, respirator, and a face shield or goggles, were worn to comply with the permit conditions for applying oxydemeton-methyl. The mixing/loading operation was conducted with a closed system. This protective clothing regime and the closed mixing/loading system approximates the requirements on the current Ovasyn® with the exception of the use of a respirator, chemical resistant coveralls, and hat. However, the Ovasyn® label requires three layers of clothing for some regions of the body (work clothes, coveralls and chemical resistant apron) which will compensate for this difference. The respirator was worn solely for protection and did not effect the monitoring of the air levels for oxydemeton-methyl.

Surgical gauze patch dosimeters were placed at several locations both under the cloth coveralls (protected) and on the outside of the rainsuit (unprotected). Hand exposure was measured using hand washes and knit nylon gloves worn underneath the chemical resistant gloves. The chemical resistant gloves were worn during mixing/loading but not during application. Personal air sampling pumps were worn by the workers to sample the air concentration of oxydemeton-methyl in their breathing zone. There were four applications made with a tractor with an enclosed cab, 17 applications made with tractors with open cabs and three applications were made with aircraft. The residues detected on the patch dosimeter represented the exposure per cm^2 that occurred to that region of the body. A body surface area of 17,689 cm^2 (excluding the hands) was used to calculate the dermal exposure for an adult male (Popendorf and Leffingwell, 1982).

The dermal exposure to the worker was estimated from the residues detected on the protected dosimeters. Most of the dosimeters located under the protective clothing had no detectable residues. Dosimeters with no detectable residues were assumed to have residues at 1/2 the minimum detectable level (MDL = 0.2 ug/sample). Exposure was expressed as the dermal exposure per hour of work or the exposure per pound of a.i. applied. The mean (arithmetic) exposure rate for an operator mixing/loading and driving a tractor with an open cab was 39.8 ug of dermal exposure per pound of a.i. applied. The values for the shoulders, forearms and shins were doubled to account for the difference in protection between cloth coveralls and chemical resistant coveralls. The mean value listed in Table IV was derived with the assumption that a

grower would treat 100 acres of cotton per day at the maximum label rate (1.0 lb. a.i./acre). Only six of the 24 exposure periods monitored for air levels of oxydemeton-methyl had detectable levels (0.76 ug/m^3 to 4.8 ug/m^3). As the vapor pressure of oxydemeton-methyl is approximately 75X greater than amitraz, the inhalation exposure when respirators are worn was considered miniscule.

B. Aerial Application

Maddy *et al.* (1979) conducted a study monitoring the occupational exposure for pilots, mixer/loaders and flaggers applying tributyl phosphorotrithioate (DEF®) and tributyl phosphorotrithioite (Folex®) to cotton in the San Joaquin Valley. The employees of two aerial application PCOs were monitored for dermal and inhalation exposure while treating 1,000 acres per day at a rate of 1.32-1.50 lbs. a.i. per acre. This would be considered a maximum exposure work schedule.

Each company utilized a closed system to mix the pesticide batches and load them into the airplanes. The workers wore work clothes and the designated protective clothing for the following tasks: mixer/loader-overalls, rubber gloves, rubber apron (company two only) boots and cap; pilots-helmets; and flaggers-coveralls and caps. These protective clothing regimes approximate the protective clothing required on the Ovasyn® label for mixer/loaders and pilots with the exception of the requirement for mixer/loaders to wear protective eyewear and the pilots to wear chemical resistant gloves when entering and exiting a contaminated aircraft. However, federal and California regulations consider flagging to be a work task that is included in the definition of "handlers" or "handling". As flaggers will be exposed to the diluted pesticide, they are required to wear coveralls over long-sleeved shirt and long pants, chemical resistant gloves, chemical resistant footwear plus socks, protective eyewear and chemical resistant head gear.

Dermal exposure was measured with the use of two layered patches (outer layer-cloth, inner layer gauze) attached on the outside of the worker's clothing. Exposure for the exposed areas (face, neck) was calculated as the sum of the residues detected on both patches. Exposure for protected body regions (arms, torso, legs) was derived from the amount of residues detected on the gauze layers. The hands were rinsed with ethyl alcohol at the end of the work shift to determine hand exposure. Inhalation exposure was measured with an air pump that drew air through sampling tubes at a flow rate of 0.2 L/minute. Six workdays were monitored with the following number of replicates for each work task: mixer/loader (10); pilot (11); and flagger (11).

A mean dermal exposure rate per pound of a.i. applied was derived from Table VI of the study (Maddy *et al.*, 1979) for the following work tasks: 11.4±7.60 µg-mixer\loader; 6.18±2.63 µg-pilot; and 7.95±5.97 µg-flagger. For inhalation the mean exposure rates per pound of a.i. applied were: 0.37±0.30 µg-mixer\loader, 0.17±0.27-pilot and 1.01±1.85 µg-flagger. The pounds of amitraz handled per workday were calculated as treating 1,000 acres per day at the maximum label rate of 1.0 lb. a.i. per acre. The exposure rates from the surrogate study were then used to derive the exposure values for amitraz listed in Table IV. A second correction was necessary for the flaggers to account for the additional protective clothing (chemical resistant gloves and hat, coveralls, protective eyewear) required by the current Ovasyn® label. Exposure to the hands accounted for 39% of the dermal exposure, the body regions protected by coveralls accounted for

23% of the dermal exposure and the head, face and neck, 38% of the exposure (Maddy *et al*., 1984). Chemical resistant gloves and cloth coveralls can provide 90% protection (Thongsinthusak *et al.*, 1993).

C. Cotton Scouts

Many growers practice IPM to control insect pests in cotton. Growers contract pest control advisors (PCAs) to check their crop through the growing season for a cost per acre fee. PCAs or field checkers under their supervision can enter fields weekly to monitor insect populations and to determine the maturity of the crop. They average at most 6 hours per workday walking in the cotton fields with the remaining time spent completing paper work and driving from one ranch to another (Dong, 1990). The potential dermal exposure for field checkers checking amitraz treated cotton can be estimated if the DFR are known at the time of entry and a transfer factor (potential dermal exposure divided by the observed DFR) can be calculated for the work activity. A transfer factor of 11,610 cm^2/hour was derived for cotton scouts from the review of exposure studies for similar activities (Dong, 1990).

Data on the deposition and degradation of amitraz residues on cotton leaf surfaces were not submitted with the cotton registration request. However, a study was conducted on pear tree foliage in Washington State to determine the amitraz derived residues present after two applications of Mitac® WP (Brady, 1992). The applications were made 14 days apart at the maximum label rate of 1.5 lbs. a.i. per acre with the last treatment occurring 14 days before the normal harvest date. A DFR value of 0.69 ug/cm^2 was observed 24 hours after the second application. Since the maximum label rate for cotton is 1.0 lb. a.i. per acre, the estimated DFR one day after an application was reduced proportionally to 0.46 ug/cm^2. The 11,610 cm^2/hour transfer factor multiplied by the DFR of 0.46 ug/cm^2 from the pear study with a six-hour exposure period yielded a potential dermal exposure of 32.0 mg per day for field checkers scouting amitraz treated cotton. Assuming the work clothing worn by the field checkers provides 90% protection (Thongsinthusak, 1991), the estimated daily dermal exposure is 3.2 mg.

Although inhalation exposure to amitraz was not estimated for the cotton scouts, it is not likely to be a significant route of exposure. A study by Wolfe (1976) surveyed the results of many exposure studies for workers mixing, loading and applying a variety of pesticides in various formulations. As part of the total exposure for the worker, the inhalation component accounted for less than 1% (mean value) with a range of 0.1-3.1 percent for the studies reviewed.

Table IV. Occupational Exposure for Workers Making Applications Of Amitraz and Scouts Checking Amitraz Treated Cotton.

Work Tasks	Daily Dermal Exposure (mg/workday)	Daily Inhalation Exposure (mg/workday)	Absorbed Daily Dose[a] (ug/kg/day)	Annual Average Daily Dose[b] (ug/kg/day)	Lifetime Average Daily Dose[c] (ug/kg/day)
Ground Application					
mix/load/apply	3.98±2.35	N/A	7.23	0.32	0.17
Aerial Application					
mix/load	11.4±7.60	0.37±0.30	23.1	0.51	0.27
apply	6.18±2.63	0.17±0.27	12.3	0.27	0.14
flag	3.51±02.64	1.01±1.85	13.0	0.29	0.16
Cotton scout	3.2	-----	7.1	0.21	0.11

Haskell, WH&S, 1994.

N/A - Not available.

[a] Dermal absorption is 13.8% (Stewart, 1993). Inhalation absorption was considered as 50% uptake and 100% absorption (Raabe, 1988). The workers in the surrogate DEF® study were all males and the surface areas of the body regions used to extrapolate exposure were appropriate for male subjects. Therefore, the weight of a 76-kg man was used to calculate the Absorbed Daily Dose (Thongsinthusak *et al.*, 1993). However, since the exposure data for the cotton scouts was derived with a transfer factor whose source of exposure data could be male or female subjects, a 62 kg body weight was used for the cotton scouts (Thongsinthusak *et al.*, 1993).

[b] Custom ag-chemical applicators servicing cotton growers could make ground applications of Ovasyn® a maximum of 16 workdays per season (Huckins, 1994). The 8 annual application days for the mixer/loader, pilot and flagger were estimated from application data of an aerial applicator in the Southern San Joaquin Valley making August treatments of Curacron® to cotton. Cotton scouts were estimated to enter amitraz treated cotton fields for 11 workdays per season. This exposure scenario is estimated from mid-July through August applications of Ovasyn® to control white flies that cause "sticky cotton" and the assumption that 25% of the cotton acreage checked by the cotton scout on a weekly basis would be treated with Ovasyn®.

[c] Calculated on the basis of a 75-year life span with 40 years of employment.

IV. Livestock Treatment

Amitraz is registered under the trade name Taktic® for use as a spray, spray-dip application on beef and dairy cattle and pigs to control ticks, mites and lice. Applications to cattle are made as a mixture of one-two cans (25.7 oz. each) per hundred gallons of water (0.4-0.8% solution by weight). Each animal can be treated with a maximum of two gallons of spray mixture. Beef cattle are usually treated for lice and ticks in the summer and fall when they are moved off the dry land pasture or range for the season. Ranchers can pen the animals and then walk them single-file past a power sprayer operator that treats one side of the animal at a time. The process is repeated until the whole body of the animal is treated (Patterson, 1994). In feedlots animals are usually treated upon arrival and large numbers of animals are treated at one time. To facilitate the rapid treatment of the cattle for lice or ticks, most feedlot operators now use other active ingredients that can be injected into the animals (Norman, 1994). However, a few operators may utilize a squeeze chute equipped with nozzles to spray the whole animal with amitraz. Another method uses a hydraulic cage to dip the animal in the spray mixture. In the dairy industry, wide spread use of this product is not known. Dairy cattle rarely get ticks but lice and parasitic fly infestations can be a problem. The U.C. Cooperative Extension dairy specialist

indicates that treatments to control lice and ticks are usually made with "over-the-counter" products formulated with coumaphos or abamectin (Maas, 1994). Products that can be injected or poured directly on the animal are easier to use than products that need to be applied as a full coverage spray.

In swine production, applications of Taktic® can be used as a preventive treatment for infections of body lice. Swine and their pens are treated with a mixture of one can of product per 50 gallons of water (0.8% solution by weight). The adult pigs are treated with a coarse spray until run off while piglets or weaners can be dipped in the mixture. In commercial operations sows are bred twice a year and moved to the farrowing barn a few days before the anticipated birth (Farley, 1994). The sows remain there for 14-28 days after the birth to nurse the piglets. When they are removed from the farrowing barn, another set of pregnant sows is moved in to give birth. In most operations, sows can be present in the farrowing barns year round. Sows can be treated for body lice when they are moved to the farrowing barns to prevent infections from spreading to the soon-to-be-born piglets (Norman, 1994). A small farm operation with 250 sows, will move approximately 40 sows per month through the farrowing barn, with about 10 arriving per week (Farley, 1994). On small farms, applications are made with either a hand-held sprayer or backpack sprayer. On larger operations, some type of power sprayer is used to make the treatments. Assuming a sow has about one half the surface area of a cow, one gallon of spray mix (1/2 oz of Taktic® in one gallon of water) containing 0.0037 lb. of amitraz would be the maximum treatment per sow. Because of the intensive labor involved, the practice of dipping piglets in the mixture is seldom used.

To estimate the occupational exposure to amitraz from applications of Taktic®, an exposure study from the application of cyromazine in a poultry house was used. Larvadex® 2SL was applied to manure piles with a hand-held sprayer, a backpack sprayer and with a hand-held boom attached to a portable power sprayer with a long hose (Haskell *et al*., 1993). Each replicate consisted of mixing and applying a two-gallon mixture of 0.1% cyromazine three times. Nine replicates of each application method were conducted with 0.024 kg of a.i. applied per replicate. The study observed potential and actual exposure when workers wear a dust mask and rubber gloves in addition to work clothing (socks and shoes, long pants and long-sleeved shirt). This protective clothing regime approximates the label requirements for handling Taktic® with the exception of the requirement to wear goggles, a hat and boots and a chemical resistant apron when mixing/loading Taktic®. Dermal exposure was detected with patches attached outside the workers Tyvek® coveralls and with cotton gloves worn underneath the rubber gloves. Pesticide residues that penetrated the cloth covering of the patches were considered actual dermal exposure. A body surface area of 19,400 cm^2 was used to calculate the total dermal exposure from the patch dosimetry and the hand washes. Respiratory exposure was monitored during the exposure period with a personal air pump that drew air through two filters covered with the dust mask material. The flow rate through the filters was two liters per minute.

The mixing/loading of the portable power sprayer and the application of the mixture with a hand-held boom to the manure piles were considered separate tasks. Exposure was expressed in milligrams of dermal exposure per replicate and the workday exposure was derived from the number of replicates (14) that could be completed during an eight hour shift. The minimum

detectable level (MDL) for cyromazine on the patches was 0.001 ug/cm^2 and 0.2 ug total for the gloves and the foam filters. All the protected patches for the workers performing the mixing/loading work task had residues below the detection limits with the exception of one. Exposure was assumed to be 1/2 the MDL when dosimeters yielded non detectable residues. Most of the workers applying cyromazine with the hand-held boom portable power sprayer had detectable residues on the thighs, ankles and forearms. The estimated exposure to cyromazine when one worker performed both the mixing/loading and application work tasks for eight hours was 3.97 mg of dermal exposure and 0.05 mg of inhalation exposure.

The Larvadex® 2SL exposure study can be used to estimate the occupational exposure to amitraz from an application of Taktic®. The workers handled 2.46 lbs. of cyromazine per workday operating the power sprayer and experienced a combined total of 3.97 mg of dermal exposure and 0.05 mg of inhalation exposure. Assuming one worker performed both work tasks during the livestock treatments, the exposure rate was equivalent to 1.61 mg of dermal and 0.02 mg of inhalation exposure per pound of active ingredient handled. The exposure rates for the backpack sprayer were 31.6 mg of dermal and 0.032 mg of inhalation exposure per pound of active ingredient handled. The handheld sprayer experienced 0.66 mg of dermal and 0.033 mg of inhalation exposure per pound of active ingredient handled.

On a small cow-calf operation, one worker could be expected to treat about 50 cows per day with a power sprayer (average herd size in Siskiyou County-150 head) (Beck, 1994). However, on larger cow-calf operations, 200 animals can be treated per day using the directed spray method with penned animals (Patterson, 1994). At the maximum Taktic® label rates for cattle, approximately 0.0075 lb. a.i. is needed to treat one grown cow. The worker on the small cow-calf operation would handle 0.375 lb. of amitraz per workday (50 X 0.0075 lb. a.i. per cow) and experience an estimated 0.60 mg of dermal exposure and 0.0075 mg of inhalation exposure. The worker on the large operation would treat 200 cows per day and experience an estimated 2.42 mg of dermal exposure and 0.03 mg of inhalation exposure. Since feedlot applications are essentially mechanized, exposure to the operator is expected to be insignificant.

For swine production, a small farm operation may use a backpack sprayer to make the Taktic® treatments while a corporate operation would probably use the power sprayer. The estimated maximum label treatment for swine on the Taktic® label was 0.0037 lb. of amitraz per animal. The small farm operation may run 250 sows while a large corporate operation can manage 10,000 sows (Koenig, 1994). On the large operations, the sow populations are divided into management "units" of about 1200 animals with each unit having its own labor force. If the sows are treated each time they enter the farrowing barn, the number of sows moving into the farrowing barn each week can be estimated by dividing the herd size or "unit" size by 52 (52 weeks per year) and then multiplying this value by two (enter twice a year). This value multiplied by 0.0037 lb. a.i. will provide an estimate in the pounds of amitraz handled per workday. Utilizing the listed dermal and inhalation exposure rates per pound of amitraz handled, the estimates for the daily and lifetime occupational exposure to amitraz from livestock treatments were derived and listed in Table V.

Table V. Lifetime Occupational Exposure to Amitraz From Livestock Treatments

Type + Size of Operation	Daily Dermal Exposure (mg/workday)	Daily Inhalation Exposure (mg/workday)	Absorbed Daily Dose[a] (ug/kg/day)	Annual Average Daily Dose[b] (ug/kg/day)	Lifetime Average Daily Dose[c] (ug/kg/day)
Cow-calf operation					
small	0.60	0.0075	1.14	0.009	0.0048
large	2.42	0.03	4.59	0.16	0.085
Swine production					
small farm	1.17	0.0012	2.13	0.30	0.16
corp. farm	0.27	0.0034	0.51	0.07	0.037

Haskell, WH&S, 1994.

[a] Dermal absorption is 13.8% (Stewart, 1993). Inhalation absorption was considered as 50% uptake and 100% absorption (Raabe, 1988). The workers in the surrogate Larvadex® study were all males and the surface areas of the body regions used to extrapolate exposure were appropriate for male subjects. Therefore, the weight of a 76-kg man was used to calculate the Absorbed Daily Dose (Thongsinthusak *et al.*, 1993).

[b] The annual number of application days for the cow-calf operator was estimated by dividing the herd size (Siskiyou County average size 150 head, large operation 2500 head) (Beck, 1994) by the number of animals treated per workday (50 or 200). If both the small and large farm operations make one treatment each week, the annual number of application days for swine production was 52.

[c] Calculated on the basis of a 75 year life span with 40 years of employment.

V. HARVESTERS

Pears are normally harvested by hand and exposure to the harvesters must be considered in the exposure assessment. An exposure study for harvesters has not been conducted for amitraz. However, an estimate of dermal exposure can be made if the dislodgeable foliar residues (DFR) at the time of harvest are known and a transfer factor (dermal exposure per worker in ug/hour divided by the DFR) can be estimated for the particular work activity.

The deposition and degradation of amitraz residues on leaf surfaces has been studied. In 1991, a study was conducted on pear tree foliage in Washington State to determine the amitraz derived residues present after two applications of Mitac® 50 WP (Brady, 1992). The applications were made 14 days apart at the maximum label rate of 1.5 lbs. a.i. per acre with the last treatment occurring 14 days before the normal harvest date. Foliage samples, consisting of 40 one-inch diameter leaf punches (405 cm^2 total surface area) each, were taken just prior to the first application and at 0, 1, 2, 5, 7, 14, 21, 28 and 35 days after the last treatment. Three samples of treated foliage and a untreated control sample were taken at each time interval. Foliage samples were spiked in the lab, frozen and shipped to the field trial site. The spiked samples of either amitraz, BTS-27271 or BTS-27919 were then included with the field and control samples at each of the sample intervals. All samples were put on dry ice and stored frozen in a field trial freezer until shipment to the analytical lab for extraction and analysis.

Analysis of all the samples was done at the NOR-AM Research center in North Carolina. The leaf discs were washed with buffered detergent solution and the rinsate partitioned with methylene chloride and evaporated to dryness. The dry residue was reconstituted with toluene and quantified by gas chromatography using a nitrogen specific detector. Samples were analyzed for the parent compound and two degradates, BTS 27271 and BTS 27919. Two "field spikes" and two spikes of the reagent used to wash the DFR off the leaf discs were analyzed for each set of leaf punch samples. The recovery of the reagent spikes averaged 98%. Recovery from the "field spikes" averaged 92.8% indicating the residues of amitraz and its degradation products were stable under the storage conditions.

The data indicate that the foliar residues of amitraz dissipate slowly. The regression of residues on time through the 35-day dissipation period yielded the following equation: $y = -0.25958 + (-0.02909\ x)$ where y = log (natural) of ug/cm^2 and x = days. Since the pre-harvest interval is seven days, a DFR of 0.63 ug/cm^2 was derived from the best-fit curve for the DFR dissipation through 35 days.

A transfer factor derived from exposure and DFR data can provide an estimate of the amount of foliage contacted per hour for workers hand-harvesting pears in an amitraz-treated orchard. A generic transfer factor was derived from three studies that observed the exposure to farm workers wearing work clothing and harvesting peaches in orchards treated with various pesticides (Table VII). The 4,023 cm^2/hour transfer factor was used in conjunction with the DFR of 0.63 ug/cm^2 from the amitraz study to calculate the dermal exposure for workers picking pears in an amitraz-treated orchard. The transfer factor times the DFR yields an estimated dermal exposure of 2,535 ug/hour or 20.3 mg/8-hour day. The respiratory exposure for the peach harvesters was minute, accounting for approximately four tenths of one percent of the total dermal exposure. This same observation has been made in other harvester exposure studies. Since the respiratory component of the total exposure is so small, it will be considered negligible for the pear harvesters.

Table VI shows the estimated exposure for harvesters working 8 hours per day in a pear orchard treated previously with 3.0 lbs. a.i. of amitraz per acre. The DFR are assumed to be 100% dislodgeable.

Table VI. Harvester Exposure to Amitraz in a Pear Orchard Treated with Amitraz.

Dermal Exposure (mg/8-hr day)	Absorbed Daily Dosage[a] (ug/kg/day)	Annual Average Daily Dosage[b] (ug/kg/day)	Lifetime Average Daily Dosage[c] (ug/kg/day)
20.3	36.9	3.64	1.94

Haskell, WH&S, 1993.

[a] Dermal absorption is 13.8% (Stewart, 1993). Inhalation exposure is negligible. Calculated for the weight of a 76-kg man (Thongsinthusak *et al.*, 1993).

[b] Calculated on the basis of 36 exposure days per year. Determined from discussions with staff of Lake and Sacramento County Agricultural Commissioners.

[c] Estimated lifetime exposure from picking pears for 40 years over a 75 year life-span.

VI. Veterinarians

A product is available for use by veterinarians to control tick infestations on dogs with collars impregnated with amitraz. The typical pet collar weighs one ounce and contains 9% amitraz by weight. Exposure to amitraz from placing the collar around the neck of the animal is expected to be miniscule due in part to the small dose of a.i. (2.6 gm) being handled. Data from research conducted for the federal registration of the Taktic® Dairy Collar indicate the release of amitraz from the polymer collar is less than 6% over a 90-day period under laboratory conditions (Nor-Am Chemical, 1991). The manufacturer recognizes this release rate could be enhanced by the abrasion of the cow's hair against the collar. Research from similar formulations indicates the maximum release rate over a 90-day period could be 20% of the a.i. present in the collar. Assuming the same release rate for the dog collar, 20% of the 2.6 gm of a.i. present in the collar could be available with an average of 5.8 ug present per day over the 90 day period. If the dog handler experienced the maximum dose of amitraz available while placing the collar on the animal with bare hands and treated five dogs per day, the absorbed daily dose (13.8% dermal absorption) would be 0.05 ug/kg/day for a 76 kg man.

REFERENCES

BFC Chemicals 1981. Medical management for Mitac® EC and Mitac® WP DPR Registration Doc. No. 287-031.

Beck, E. Agricultural Inspector Siskiyou County 1994. Personal conversation on October 13.

Brady, S. S. 1992. Determination of amitraz-derived dislodgeable residues on pear foliage following two applications of Mitac® WP 14 days PHI. DPR Registration Doc. No. 287-084.

Campbell, J. K. 1984a. A comparison of the metabolism of ^{14}C amitraz in the rat, mouse, baboon and human. DPR Registration Doc. No. 287-041.

Campbell, J. K. 1984b. Excretion and tissue residues of ^{14}C amitraz in a male and female baboon given a single oral dose of 10 mg ^{14}C amitraz per kg of body weight. DPR Registration Doc. No. 287-041.

Campbell, J. K. and Needham, D. 1983. Excretion and tissue residues of ^{14}C amitraz in male and female mice given a single oral dose of 10 mg ^{14}C amitraz/kg body weight. DPR Registration Doc. No. 287-041.

Campbell, J. K. and Needham, D. 1984a. Dermal absorption of ^{14}C amitraz in emulsifiable concentration formulation by male and female pigs given a single topical application of 18 mg active ingredient. DPR Registration Doc. No. 287-041.

Campbell, J. K. and Needham, D. 1984b. Urinary excretion of ^{14}C amitraz by two male humans following a single oral dose of 0.25 mg/kg of body weight. DPR Registration Doc. No. 287-041.

Campbell, J. K. and Needham, D. 1984c. The metabolism of ^{14}C amitraz by male and female rats. DPR Registration Doc. No. 287-041.

Castro, L. and Ramos, M. 1988. Exposure of spray operator to amitraz during air blast application of Mitac® WP to pear trees. DPR Registration Doc. No. 287-069.

CDFA 1985. Summary of reports from physicians of illnesses that were possibly related to pesticide exposure during the period January 1 - December 31, 1984 in California. WH&S Branch Report HS-1304.

CDFA 1986. Summary of reports from physicians of illnesses that were possibly related to pesticide exposure during the period January 1 - December 31, 1985 in California. WH&S Branch Report HS-1370.

CDFA 1987. Summary of illnesses and injuries reported in California by physicians as potentially related to pesticides 1986. WH&S Branch Report HS-1418.

CDFA 1990. California Department Food and Agriculture's Summary of County Agricultural Commissioners' Reports, 1990-1991.

Challis, I. R. 1990. Dermal absorption of amitraz in the rat. DPR Registration Doc. No. 287-084.

Dong, M. H. 1990. Dermal transfer factor for cotton scouts. A memorandum dated June 8. WH&S, CDFA.

DPR 1993. Annual pesticide use report-1991.

DPR 1993a. Summary of illness and injuries reported by California physicians as potentially related to pesticides 1990. WH&S Branch Report HS-1666.

DPR 1994. Annual pesticide use report-1992.

DPR 1994a. Pesticide illness surveillance program summary report 1991. WH&S Branch Report HS-1692.

DPR 1994b. Pesticide illness surveillance program summary report 1992. WH&S Branch Report HS-1702.

DPR 1995. Annual pesticide use report-1993.

DPR 1995a. Pesticide illness surveillance program summary report 1993. WH&S Branch Report HS-1724.

Edmiston, S., and Richmond, D. 1988. California summary of illness and injury reported by physicians as potentially related to pesticides 1987. WH&S Branch Report HS-1493.

Farley, J. Tulare County Farm Advisor 1994. Personal conversation of October 20.

Goodell, P. IPM Cotton Advisor-San Joaquin Valley 1993. Personal conversation on June 25.

Hacker, L. A. 1992. Monitoring of the metabolites of amitraz in urine of spray operators applying Mitac® WP to pear trees in Washington. DPR Registration Doc. 287-084

Haskell, D., Dong, M., and Thongsinthusak, T. 1993. Estimation of exposure of persons in California to pesticide products that contain cyromazine. DPR, Worker Health & Safety Branch Report HS-1645.

Huckins, W. 1994. Personal conversation on June 21. Pesticide salesman for pest control operator.

Hornish, R. E. and Nappier, J. M. 1983. The absorption, metabolism and excretion of Mitaban® (U-36,059) in the dog from oral and dermal exposure. DPR Registration Doc. No. 287-041.

Kakuk, T. J. and Weddon, T. E. 1976. U-36059-safety evaluation of BAAM® 1.5 EC in dogs following a single topical exposure. DPR Registration Doc. No. 287-012.

Knowles, C. O., and Benezet, H. J. 1981. Excretion balance, metabolic fate and tissue residues following treatment of rats with amitraz and N'-(2,4-dimethylphenyl)-N-methylformamidine (BTS 27271). DPR Registration Doc. No. 287-041.

Koenig, J. Tulare County Farm Advisor 1994. Personal conversation on October 21.

Maas, Dr. University of California Cooperative Extension dairy specialist 1994. Personal conversation on October 11.

Maddy, K., Peoples, S., Datta, P., Johnston, L., Smith, C., Conrad, D., and Cooper, C. 1979. Monitoring of potential exposures of mixer/loaders, pilots, and flaggers during application of tributyl phosphorotrithioate (DEF®) and tributyl phosphorotrithioite (Folex® to cotton fields in the San Joaquin Valley of California. DPR, WH&S Branch Report HS-676.

Maddy, K. T. Wang, R. G., and Winter, C. 1984. Dermal exposure monitoring of mixers, loaders and applicators of pesticides in California, 1984. DPR, WH&S Report HS-1069.

Mehler, L., Edmiston, S., Richmond, D., O'Malley, M., and Krieger, R. 1990. Summary of illness and injuries reported by California physicians as potentially related to pesticides 1988. WH&S Branch Report HS-1541.

Mehler, L. 1991. Summary of illness and injuries reported by California physicians as potentially related to pesticides 1989. WH&S Branch Report HS-1624.

Nor-Am Chemical 1991. Taktic® Dairy Collar: For control of lice on dairy cattle. DPR, Pesticide Registration Branch Library Doc. No. 287-080.

Norman, B. Veterinary Medicine Cooperative Extension Specialist University of California, Davis 1994. Personal conversation on October 18.

Oshita, C. M., Schneider, F. A., and Margetich, S. 1988. An exposure study of mixer/loaders and applicators using oxydemeton-methyl (Meta-Systox R®) in the Salinas and Santa Maria Valleys of California in 1986. DPR, WH&S Branch Report HS-1398.

Patterson, F. Doctor Veterinary Medicine-California Department of Food and Agriculture 1994. Personal conversation on October 11.

Popendorf, W. J., Spear, R. C., Leffingwell, J.T., Yager, J., and Kahn, E. 1979. Harvester exposure to Zolone® (phosalone) residues in peach orchards. *Journal of Occupational Medicine*, Vol. 21, No. 3, pg 189-194.

Popendorf, W. J. and Leffingwell, J. T. 1982. Regulating OP pesticides residues for farmworker protection. *Residue Reviews*. Vol. 82, pg 125-201.

Raabe, O. G. 1988. Inhalation uptake of xenobiotic vapors by people. Final Report, California Air Resources Board.

Rech, C. 1989. Omite® 30W on peaches-worker reentry. Department of Pesticide Regulation, Pesticide Registration Library Doc. No. 259-080. Memo to Terry Schmer, March 3, 1989.

Spencer, J. R., Hernandez, B. Z., Schneider, F. A., Margetich, S. S., Begum, S., and Wilson, B. W. 1993. Dermal and urinary monitoring of peach and apple harvesters exposed to

organophosphate residues in Sutter, Stanislaus and Madera Counties, 1989 and 1990. Department of Pesticide Regulation, Worker Health and Safety Branch Report HS-1577.

Stewart, F. P. 1993. ^{14}C-amitraz: dermal absorption in the rat. DPR, Pesticide Registration Library Doc. No. 287-104.

Thongsinthusak, T., Brodberg, R., Ross, J. Krieger, R., and Gibbons, D. 1991. Developing pesticide exposure mitigation strategies for handlers and harvesters. DPR, WH&S Report HS-1631.

Thongsinthusak, T., Ross, J., and Meinders, D. 1993. Guidance for the preparation of human pesticide exposure assessment documents. DPR, WH&S Report HS-1612.

Upjohn Company 1976. Application for new pesticide product registration, BAAM® EC Miticide-Insecticide·DPR Registration Document No 287-004.

U. S. EPA 1979. Amitraz (BAAM®) Position Document 4. DPR Registration Library.

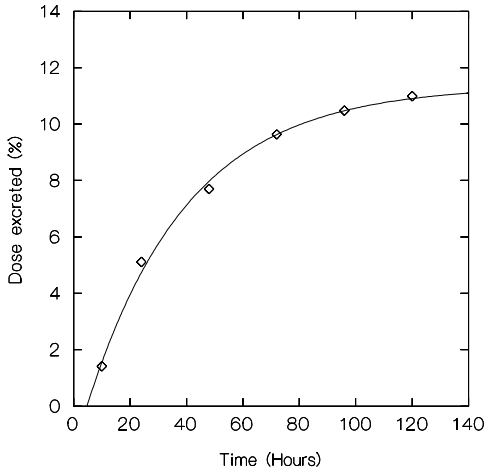
U. S. EPA 1987a. Guidance For the Reregistration of Pesticide Products Containing Amitraz As the Active Ingredient. DPR Registration Library.

U. S. EPA 1987b Office of Pesticide Programs. Procedure for studying dermal absorption.

Wolfe, H. R. 1976. Field exposure to airborne pesticides in air pollution from pesticides and agricultural processes. ed. Lee, R. E. Jr. *CRC Press*, Cleveland, Ohio.

Figure 1. Asymptotic plot of percent dose excreted in urine and feces after topical administration of amitraz at 0.1 mg/animal (ca 10 µg/cm^2)

$$Y = 11.356*(1-EXP(-0.028*(X-4.738)))$$



Statistics:

WED 10/26/94 10:09:05 AM C:\TCSYS\AMITRZ1D.SYS

ITERATION	LOSS	PARAMETER VALUES		
0	.4021768D+03	.1000D+00	.1000D+00	.1000D+00
1	.3014362D+03	.6667D+01	.1067D+01	-.4833D+01
2	.6787968D+02	.7453D+01	.8223D+00	-.4994D+01
3	.4288598D+02	.8078D+01	.1604D+00	-.4593D+01
4	.1483351D+02	.8776D+01	.5133D-01	-.4969D+01
5	.6958837D+01	.1015D+02	.5252D-01	-.5953D+01
6	.5753622D+00	.1118D+02	.3192D-01	-.6662D+01
7	.4512091D+00	.1104D+02	.3220D-01	-.6561D+01
8	.4500136D+00	.1104D+02	.3225D-01	-.6565D+01
9	.4496657D+00	.1104D+02	.3224D-01	-.6562D+01
10	.4466517D+00	.1100D+02	.3214D-01	-.6468D+01
11	.4342199D+00	.1092D+02	.3254D-01	-.6168D+01
12	.3769090D+00	.1121D+02	.3089D-01	-.5815D+01
13	.2552073D+00	.1135D+02	.2848D-01	-.4920D+01
14	.2446734D+00	.1138D+02	.2785D-01	-.4646D+01
15	.2429564D+00	.1135D+02	.2816D-01	-.4748D+01
16	.2429082D+00	.1136D+02	.2811D-01	-.4737D+01
17	.2429066D+00	.1136D+02	.2811D-01	-.4737D+01
18	.2429065D+00	.1136D+02	.2811D-01	-.4738D+01
19	.2429065D+00	.1136D+02	.2811D-01	-.4738D+01

DEPENDENT VARIABLE IS RECOV

SOURCE	SUM-OF-SQUARES	DF	MEAN-SQUARE
REGRESSION	410.741	3	136.914
RESIDUAL	0.243	3	0.081
TOTAL	410.983	6	
CORRECTED	68.424	5	

RAW R-SQUARED (1-RESIDUAL/TOTAL) = 0.999
CORRECTED R-SQUARED (1-RESIDUAL/CORRECTED) = 0.996

PARAMETER	ESTIMATE	A.S.E.	LOWER <95%>	UPPER
MAX	11.356	0.357	10.218	12.493
RATE	0.028	0.003	0.018	0.038
LAG	-4.738	1.272	-8.785	-0.691

ASYMPTOTIC CORRELATION MATRIX OF PARAMETERS

	MAX	RATE	LAG
MAX	1.000		
RATE	-0.872	1.000	
LAG	0.479	-0.712	1.000

(TCW/Dermal/Amitrz1W)

Figure 2 Metabolism of a 100 mg/kg Body Weight Oral Dose of ^{14}C-Amitraz in Rats

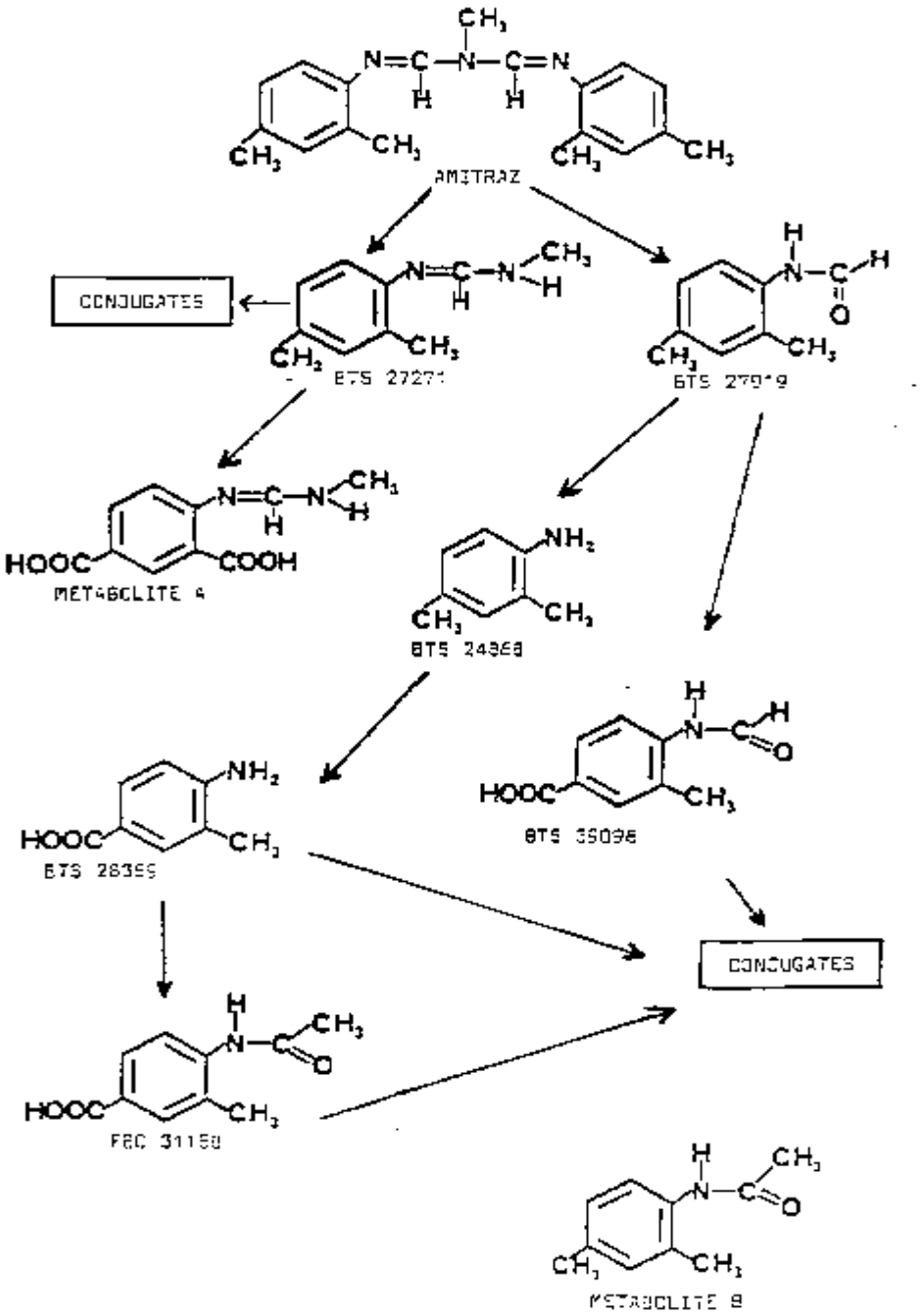


Table VII Estimation of a Generic Transfer Factor For Tree Crop Harvesters From Dermal and Dislodgeable Foliar Residue Data

Pesticide and year applied(a)	Crop and application site	No. of days post application(b)	Observed DFR (μg/cm2)(c)	No. of workers Monitored(d)	Mean dermal exposure per harvester (mg/8 hour workday)	Transfer factor for harvesters (cm2/hour)(e)	Total foliage contacted by all harvesters in crew (cm2/hour)(f)
Azinphos-methyl, 1989 (1)	Peaches Sutter County	32	0.66	ten	15.6	2958	29,600
Azinphos-methyl, 1989 (1)	Peaches Sutter County	33	0.62	ten	15.5	3,119	31,200
Azinphos-methyl, 1990 (1)	Peaches Sutter County	52	0.36	eleven	12.0	4,174	45,900
Azinphos-methyl, 1990 (1)	Peaches Sutter County	53	0.61	eleven	14.0	2,877	31,600
Azinphos-methyl, 1989 (1)	Peaches Stanislaus County	60	0.009	eight	0.44	6,111	48,900
Azinphos-methyl, 1989 (1)	Peaches Stanislaus County	61	0.011	nine	1.25	14,205	127,800
Azinphos-methyl, 1989 (1)	Peaches Stanislaus County	62	0.07	eight	4.30	7,679	61,400
Phosmet 1989 (1)	Peaches Stanislaus County	34	2.5	eight	28.17	1,409	11,300
Phosmet 1989 (1)	Peaches Stanislaus County	35	2.5	eight	31.6	1,579	14,200
Phosmet 1989 (1)	Peaches Stanislaus County	36	2.5	eight	39.3	1,964	15,700
Phosalone 1976 (2,3)	Peaches Stanislaus County	13-15	2.90	six (4)	76.0	3,276	19,700
Phosalone 1977 (2,3)	Peaches Stanislaus County	7-9	3.59	six (4)	67.2	2,340	14,000
Phosalone 1977 (2,3)	Peaches Stanislaus County	22-24	0.90	six (4)	57.2	7,944	47,700

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

Pesticide and year applied(a)	Crop and application site	No. of days post application(b)	Observed DFR (µg/cm2)(c)	No. of workers Monitored(d)	Mean dermal exposure per harvester (mg/8 hour workday)	Transfer factor for harvesters (cm2/hour)(e)	Total foliage contacted by all harvesters in crew (cm2/hour)(f)
Phosalone	Peaches						
1977 (2,3)	Stanislaus County	3-5	2.89	six (4)	111	4,810	28,900
Azinphos-methyl	Peaches						
1976 (2,3)	Stanislaus County	22-24	0.20	six (4)	12.3	7,689	46,100
Propargite	Peaches						
1988 (4)	Fresno County	34	0.59	ten	5.17	1,095	11,000
Propargite	Peaches						
1988 (4)	Fresno County	39	0.54	ten	5.55	1,285	12,900
Propargite	Peaches						
1988 (4)	Fresno County	45	0.48	ten	3.65	950	9,500

Weighted Mean Transfer Factor for all Data = Sum of Total Foliage Contacted by All Harvesters in Each Study divided by the Total Number of Workers Monitored in All Studies.
= 4023 ug^2/hour

(a) Sources of data.
(1) Spencer et al., 1993.
(2) Popendorf et al., 1979.
(3) Popendorf and Leffingwell, 1982.
(4) Rech, 1989.

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

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

(d) The number of harvesters monitored for dermal exposure with patch dosimetry for a 4-8 hour exposure period per workday.
(4) Each worker (ten total) only wore two patches and the patches were pooled at the end of workday to approximate the total dermal exposure for two workers. Therefore, each harvest day was considered two workdays.

(e) Formula for calculating Transfer Factor:
Mg of dermal exposure per workday X 1,000 ug/mg divided by observed DFR X 8 hr/day.

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

REFERENCES

Popendorf, W. J., Spear, R. C., Leffingwell, J.T., Yager, J. and Kahn, E. 1979. Harvester exposure to Zolone® (phosalone) residues in peach orchards. Journal of Occupational Medicine, Vol. 21, No. 3, pg 189-194.

Popendorf, W. J. and Leffingwell, J. T. 1982. Regulating OP pesticides residues for farmworker protection. Residue Reviews. Vol. 82, pg 125-201.

Rech, C. Worker, Health and Safety Branch. Omite 30W on Peaches-Worker Reentry. Department of Pesticide Regulation, Pesticide Registration Library Doc. No. 259-080. Memo to Terry Schmer, March 3, 1989.

Spencer, J. R., Hernandez, B. Z., Schneider, F. A., Sanborn, J. R., Margetich, S. S., Begum, S. and Wilson, B. W. 1993. Dermal and urinary monitoring of peach and apple harvesters exposed to organophosphate residues in Sutter, Stanislaus and Madera Counties, 1989 and 1990. Department of Pesticide Regulation, Worker Health and Safety Branch Report HS-1577.