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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

3-May-2002

MEMORANDUM:

SUBJECT: **Fenbutatin-oxide.** Revised Preliminary Human Health Risk Assessment. HED Chapter for the Tolerance Reassessment Eligibility Decision (TRED). Chemical No. 104601. DP Barcode D282791.

FROM: Paula A. Deschamp, M.S., Risk Assessor
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THRU: Alan Nielsen, Branch Senior Scientist
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Attached is HED's Revised Preliminary Human Health Risk Assessment for the Fenbutatin-oxide Tolerance Reassessment Eligibility Decision (TRED). This document addresses comments received from Griffin L.L.C. (6-March-2002) for error correction in accordance with Phase I of the Committee to Advise on Tolerance Reassessment and Transition (CARAT) public participation process. This revised risk assessment incorporates revised disciplinary chapters and other supporting documentation from HED's Hazard Assessment Review Committee (HIARC) and the FQPA Safety Factor Committee. The dietary, residential, and aggregate risk estimates have been modified to reflect re-evaluated hazard and exposure data according to the 2002 Office of Pesticide Programs 10X Guidance Document.

This document addresses tolerances subject to reassessment in accordance with Federal Food Drug & Cosmetic Act (FFDCA) as amended by the Food Quality Protection Act of 1996 (FQPA). The FQPA requires EPA to re-evaluate existing tolerances to ensure that children and other sensitive subpopulations are protected from pesticide risks. Because FQPA addresses only non-occupational (residential) risk concerns for food-use pesticides with established tolerances or exemptions, risks to occupational workers are not addressed in this document. The Reregistration Eligibility Decision (RED) issued for fenbutatin-oxide in September 1994, included an occupational exposure and risk

assessment as part of the Agency's conclusion that uses of fenbutatin-oxide would not cause unreasonable risk to humans or the environment.

The revised human health risk findings summarized in this assessment incorporates disciplinary chapters and other supporting documentation as follows:

Revised Tier 3 Chronic Dietary Exposure Assessment. Sheila Piper (May, 2002; D282678)

Revised Residential Exposure Assessment for Recommendations for the Tolerance Reassessment Evaluation Decision (TRED) Document for Fenbutatin-Oxide. Shanna Recore (May, 2002; D282677)

Fenbutatin-Oxide - Fourth Report of the Hazard Identification Assessment Review Committee. David G. Anderson (April 30, 2002; TXR.0050696).

Fenbutatin Oxide - Reassessment Report of the FQPA Safety Factor Committee. Brenda Tarplee (May 2, 2002)

Revised (1st) Toxicology Chapter for the TRED for Fenbutatin-oxide. David G. Anderson (14-January-2002; D272900, TXR#0050393)

The Outcome of the HED Metabolism Assessment Review Committee to Discuss degradates in Drinking Water. Sheila Piper (10-May-2001)

Residue Chemistry Chapter for the Tolerance Reassessment Eligibility Decision (TRED) Document. (1-November-2001; D272901)

Product Chemistry Chapter for the Tolerance Reassessment Eligibility Decision (TRED) Document. K. Dockter (4-September-2001; D274437)

Quantitative Usage Analysis for Fenbutatin-Oxide. Jihad Alsadek (20-September-2001)

Review of Fenbutatin-Oxide Incident Reports. Jerome Blondell (17-May-2001; D275020)

Drinking Water Assessment to Support TRED for Fenbutatin Oxide. Lucy Shanaman (31-July-2001; D275465)

RDI: BRSrSci: Nielsen (05/03/02)
P. Deschamp 812D: CM#2: (703)305-6227: 7509C: RRB2

Fenbutatin-Oxide (PC Code 104601)
Preliminary Human Health Risk Assessment
HED Chapter for the Tolerance Reassessment Eligibility Decision (TRED)

1.0 EXECUTIVE SUMMARY

Fenbutatin-oxide is an organotin acaricide effective against mites on a variety of tree nuts, fruit trees, greenhouse crops, and ornamentals, including residential sites. Fenbutatin-oxide is formulated as a wettable powder (50 percent ai) for foliar application to agricultural and commercial/residential sites by Certified Applicators only, and as an emulsifiable concentrate liquid (0.5 to 0.75 percent ai) for non-occupational application to residential sites (ornamentals).

Hazard Profile

Fenbutatin-oxide has low acute toxicity by the oral and dermal routes (Category III) and is more acutely toxic by the inhalation route (Category II). It is a severe eye irritant (Category I), but not an acute primary skin irritant (Category IV). The technical grade is not a skin sensitizer in the Buehler test in Guinea pigs. A 21-day rabbit dermal study showed no systemic toxicity, but showed skin reactions (mild to severe dermal erythema and mild edema in the treated skin and necrosis at the highest dose level tested).

A major characteristic of the hazard profile for fenbutatin-oxide is that it is highly irritating and appears to be unpalatable. Subchronic and chronic studies in rats did not provide clear evidence of any specific target organ or toxic effect. In rats, increased alkaline phosphatase was believed to be of intestinal origin and in the rabbit developmental study, histological stomach lesions were reported. All other studies in the rat, mouse, and dog showed body weight and food consumption decreases in the absence of any treatment related histological findings. There was increased susceptibility in the rat reproduction study, but not in rat and rabbit developmental studies. Fenbutatin-oxide is not a carcinogen and has been placed in Group E; no evidence of carcinogenicity in the rat or mouse and is negative for mutagenicity.

The FQPA Safety Factor Committee has re-evaluated the hazard and exposure data for fenbutatin-oxide and has recommended a 3x traditional safety factor to address data deficiencies and no additional Special FQPA safety factor. The 3x safety factor is for the lack of a subchronic neurotoxicity study to confirm brain weight decreases observed in both the 90-day rat and chronic rat studies and applies to all population subgroups and risk assessments.

All the toxicity endpoints selected for risk assessment are based on decreased offspring body weight gain observed during lactation in the 2-generation rat reproduction study. The dose level of 5.1 mg/kg/day was selected for chronic dietary, short- and intermediate-term dermal and inhalation risk assessments. Risk calculations incorporated 10% dermal absorption and 100% inhalation absorption factors for estimates of dermal and inhalation exposure, respectively. An uncertainty factor (UF) of 100 was applied to all doses selected for risk assessment purposes to account for interspecies extrapolation (10x) and intraspecies variability (10x). A 3x FQPA safety factor was retained for all risk assessments and population subgroups.

Exposure and Risk Contributions from the Food Pathway

HED did not identify any risk concerns from exposure to fenbutatin-oxide in food. Agricultural use of fenbutatin-oxide as a foliarly applied miticide is likely to result in detectable residues of parent material on raw agricultural commodities and residues are likely to be primarily on fruit surfaces. Existing tolerances for fenbutatin-oxide residues range from 0.1 ppm to 0.5 ppm in livestock commodities and from 0.5 ppm (nutmeats) to 140 ppm (citrus oil) in raw agricultural commodities (RACs) and processed food/feed items. USDA's Pesticide Data Program (PDP) analysis indicates detectable residues in 1995-1996 and in 1998 on apples, grapes, oranges, peaches, and pears. A refined (Tier 3) deterministic chronic dietary assessment was conducted using DEEM™ which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. Inputs to the dietary analysis included anticipated residues (ARs) from PDP and field trial data. Weighted average estimates of percent crop treated and processing information for apples and oranges were incorporated into the assessment. The calculated chronic dietary exposure (residue x consumption) was compared to a chronic population adjusted dose (cPAD) of 0.017 mg/kg/day, which reflects a FQPA factor of 3x for the U.S. population and all population subgroups. The chronic dietary risk estimates associated with the use of fenbutatin-oxide do not exceed HED's level of concern for any population subgroup. The chronic dietary exposure estimate for all infants <1 year of age (the highest exposed population subgroup) is 1.0% of the cPAD.

An acute dietary endpoint was not established for fenbutatin-oxide because there were no effects observed in any oral toxicity studies that could be attributable to a single exposure (dose). Therefore, an acute dietary assessment was not conducted.

Exposure and Risk Contributions from the Water Pathway

HED did not identify any chronic risk concerns from exposure to fenbutatin-oxide in drinking water. Fenbutatin-oxide is persistent but very immobile in the environment. The available environmental fate data on fenbutatin-oxide indicate that it is expected to be persistent; however, these data also indicate that fenbutatin-oxide is strongly bound to soils. This propensity towards binding precludes the possibility of significant concentrations being present in surface waters, and mitigates any potential to accumulate in ground waters. The Environmental Fate and Effects Division provided Tier II (PRZM/EXAMS) surface water modeling for fenbutatin-oxide residues using the index reservoir with the percent cropped area. The estimated environmental concentration (EEC) for a 1 in 10 year annual average concentration of fenbutatin-oxide residues in surface water is not likely to exceed 6.0 µg/L. The SCI-GROW predicted concentration of fenbutatin-oxide in ground water is not expected to exceed 0.006 μg/L.

Exposure Potential from Residential Pathways

HED did not identify any risk concerns for non-occupational (residential) handler of fenbutatin-oxide. There is a potential for dermal and inhalation exposure to adults during mixing, loading,

and application of fenbutatin-oxide liquid formulations to ornamentals in the residential setting. Fenbutatin-oxide homeowner products are typically applied using hand-held equipment such as a low pressure handwand, a backpack sprayer, or a hose-end sprayer. Post-application exposure to either adults or children is unlikely. The Pesticide Handler's Exposure Database (PHED), Outdoor Residential Exposure Task Force (ORETF) exposure studies, and the Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December, 1997) and HED Exposure SAC Policy 12 modifications (22-February-2001) were used as data sources and methods of estimating residential exposures.

Short-term dermal and inhalation risks were calculated using the Margin of Exposure (MOE) approach, which is a ratio of the exposure to the toxicological endpoint of concern. An MOE ≥300 (which includes the 3x FQPA Safety Factor) does not present a risk concern for residential handlers. Calculations based on combined dermal and inhalation risk indicate that the total MOEs are greater than 300 (the lowest MOE was 4,900) when fenbutatin-oxide is applied using either a low-pressure handwand, a backpack sprayer, or a hose-end sprayer.

Aggregate Risk Assessments

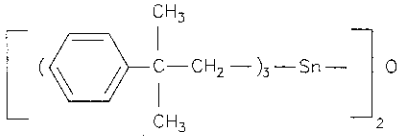
Aggregate chronic risk estimates do not exceed HED's level of concern. The aggregate chronic dietary risk estimates include exposure to residues of fenbutatin-oxide in food and water. No chronic residential use scenarios were identified. Chronic dietary exposure is 1.0% of the chronic PAD for the most highly exposed population subgroup (all infants less than 1 year) and does not exceed HED's level of concern. The estimated EECs in ground and surface water are less than the drinking water level of comparison indicating that chronic aggregate exposure to fenbutatin-oxide does not exceed HED's level of concern.

Short-term aggregate risk estimates do not exceed HED's level of concern. HED determined that based on the short-term, non-dietary toxicity profile it is appropriate to aggregate food, water, and residential pathways of exposure for assessment of short-term risks. The residential handler exposure scenario resulting in the highest total exposure potential (mixing/loading/applying liquids with a hose-end sprayer) was combined with average food exposures to calculate short-term aggregate MOEs and DWLOCs. The estimated EECs in ground and surface water are less than the DWLOCs indicating that short-term aggregate exposure to fenbutatin-oxide does not exceed HED's level of concern.

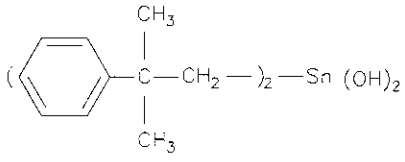
2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Chemical Structure and Identification of Active Ingredient

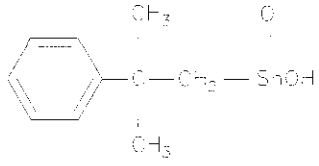
The molecular structures of fenbutatin oxide and its metabolites SD-31723 and SD-33608 are presented below:



FENBUTATIN-OXIDE



SD-31723



SD-33608

Chemical Name:	Hexakis (2-methyl-2-phenylpropyl)-distannoxane
Common Name:	Fenbutatin-oxide
PC Code Number:	104601
CAS Registry No.:	13356-08-6
Chemical Class:	Organotin
Chemical Type:	Acaricide (selective miticide)
Trade Names:	Vendex
Mode of Action:	Inhibition of oxidative phosphorylation
Empirical formula:	$C_{60}H_{78}OSn_2$
Molecular weight:	1052.66 g/Mol

2.2 Physical Properties

Fenbutatin-oxide is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal. Properties of fenbutatin-oxide such as high molecular weight and insolubility in water would markedly limit absorption through the skin. Preliminary analysis data indicate there are no impurities present in fenbutatin-oxide technical material that would contribute to the toxicity profile and thus pose a toxicological concern. A detailed list of the physical properties of fenbutatin-oxide technical is provided below:

Color:	White
Physical state:	Crystalline solid
Odor:	Odorless
MP:	145 C
Density:	0.42 g/cc @23 C
Water solubility:	12.7 ppb @ 20 C
Vapor Pressure:	$<10^{-7}$ mm Hg (negligible at room temperature)
P_{ow}:	1.4×10^{5}
Stability:	Stable for 2 yrs. @ ambient temperature; 2 wks. @ 110 C. In organic solvents in presence of water it converts to the hydroxide; in presence of acid it converts to the salt, incorporating the anion of the acid.

3.0 HAZARD CHARACTERIZATION

The toxicity database for fenbutatin-oxide, although not of high quality, provides sufficient information to adequately identify hazards for risk assessment purposes. Many of the acceptable/guideline studies were conducted prior to implementation of current guidelines and GLP requirements. The chronic study in the dog is lacking effective dosage information and is unacceptable; however, another study is not recommended by HED's Hazard Identification Assessment Review Committee (HIARC) as further testing is not expected to identify a more sensitive endpoint for risk assessment. A 28-day inhalation study in rats is required to characterize the effects of fenbutatin-oxide via the inhalation route; a confirmatory dermal penetration study is also required. The HIARC also recommended that a subchronic neurotoxicity screening battery in the rat be required to better characterize the neurotoxic potential of fenbutatin-oxide. A developmental neurotoxicity study is held in reserve, pending the results from the subchronic neurotoxicity screening battery.

3.1 Hazard Profile

Fenbutatin-oxide is an organotin acaricide with a mode of action that inhibits oxidative phosphorylation at the site of dinitrophenol uncoupling (the production of energy in the form of adenosine triphosphate, ATP). As a member of the organotin class of compounds, fenbutatin-oxide can be further characterized as an arylorganotin compound; other organotins such as trimethyltin and triethyltin are alkylorganotins. In general, the trimethyltin and triethyltin compounds are well absorbed from the gastrointestinal tract and are the most toxic in this group. Triethyltin exhibits neurotoxic effects of encephalopathy and cerbral edema. By comparison, aryl organotin compounds such as fenbutatin-oxide are insoluble and poorly absorbed and more moderate toxicities are typically exhibited.

Fenbutatin-oxide has low acute toxicity by the oral and dermal routes (Category III) and is more acutely toxic by the inhalation route (Category II). It is a severe eye irritant (Category I), but not an acute primary skin irritant (Category IV). The technical grade is not a skin sensitizer in the Buehler test in Guinea pigs. A 21-day rabbit dermal study showed no systemic toxicity, but showed skin reactions (mild to severe dermal erythema and mild edema in the treated skin and necrosis at the highest dose level tested). This later study suggests that fenbutatin-oxide causes severe skin lesions following repeated exposures.

A major characteristic of fenbutatin-oxide toxicity is the irritating nature and unpalatable properties, which cause body weight reduction before systemic toxicity is seen. Evidence of gut toxicity was seen in the chronic study in rats and dogs. In rats, increased alkaline phosphatase believed to be of intestinal origin was seen, in addition to soft stools. In the dog, frequent vomiting and diarrhea was seen at the higher dose levels, and to a less extent at lower dose levels. The developmental study in the rabbit was the only study demonstrating histological lesions of the stomach (severity not reported). All other studies in the rat, mouse, and dog showed body weight and food consumption decrease which were stated to be caused by unpalatable test material in the diet. However, reduced food efficiency was shown only at the highest dose level in the study on reproduction, with nominal reduction at the highest dose level tested (HDT) in the rat subchronic and chronic studies. No treatment related histological findings were noted in the chronic rat, mouse or dog studies. In each of these chronic studies, body weight decrease was noted but it was unclear whether this resulted from systemic toxicity, gut irritation or decreased food consumption from the unpalatability of the diet or from vomiting in the case of the dog. The failure of the chronic studies to show unequivocal systemic toxicity is probably due to poor absorption through the gut. Thus, the unpalatability or gut irritation probably limited systemic toxicity of the poorly absorbed fenbutatin-oxide in the treated animals. There is no evidence of neurotoxicity in any of the acute, subchronic or chronic/oncogenicity studies submitted. However, in an unacceptable 90-day feeding study in rats, male absolute brain weight was significantly reduced (3%) at study termination and by the same amount at the 24 month sacrifice in an acceptable rat chronic/carcinogenicity study.

There is evidence of increased susceptibility in the reproduction study, but not in rat and rabbit developmental toxicity studies with fenbutatin-oxide. In the reproduction study, reduced pup weight occurred at a lower dose level than that causing parental weight reduction. Only the parental body weight reduction at the highest dose seemed to be due to toxicity. Maternal toxicity in the rabbit developmental toxicity study appeared to be caused by irritating properties of fenbutatin-oxide. Fetal death occurred in the acceptable rabbit developmental study at the same dose levels causing death, anorexia and possible stomach lesions in the mothers. Developmental effects were not shown in the rat study at the highest dose level.

Fenbutatin-oxide did not cause cancer in carcinogenicity studies in the rat and mouse. Fenbutatin-oxide has been placed in group E; no evidence of carcinogenicity in the rat or mouse. There is also no mutagenic concern for fenbutatin-oxide in pre-1991 *in vitro* and *in vivo* mutagenicity studies.

A rat metabolism study demonstrates that fenbutatin-oxide is poorly absorbed from the gastrointestinal tract when the chemical is administered orally. Of the administered single doses, total recovered radioactivity was 83.5-98.8% from feces, <1% from urine, 0.5-3.6% from cage wash, and 0.3-0.8% from carcass and tissues. The low total radioactivity remaining in the body after 5-7 days indicated that tissue accumulation was very low. Chromatographic analysis of fecal extracts showed that unchanged fenbutatin-oxide accounted for 86-96% of the extractable radioactivity, with two minor metabolites comprising another 1-3%.

No studies are available to directly provide a dermal absorption factor. An upperbound dermal absorption factor was determined to be 10% based on a comparison of the physical-chemical characteristics of fenbutatin-oxide and triphenyltin-hydroxide (TPTH). Although the dermal absorption of fenbutatin-oxide is believed to be less than 10%, there is insufficient data to support a smaller factor.

A summary of the findings from acute toxicity tests is presented in Table 1 and a summary of the findings from the subchronic, chronic, mutagenicity and other toxicity studies is presented in Table 2.

Table 1. Acute Toxicity of Fenbutatin-oxide Technical

Guideline No./ Study Type	MRID No.	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity	40473504	LD_{50} = 4400 mg/kg	III
870.1200 Acute dermal toxicity	00112990	LD_{50} > 2000 mg/kg	III
870.1300 Acute inhalation toxicity	40473502	LC_{50} = 0.070 mg/L	II
870.2400 Acute eye irritation	00112990	Severe	I
870.2500 Acute dermal irritation	00112990	Mild	IV
870.2600 Skin sensitization	00112990	Not a dermal sensitizer in the Buehler test in Guinea pigs	NA

Table 2. Subchronic, Chronic, Mutagenicity and Other Toxicity of Fenbutatin-oxide.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rats	00037580 (1973) Unacceptable 0, 50, 100, 300 or 600 ppm M/F: 0, 2.5, 5, 15 or 30 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on elevated alkaline phosphatase.
870.3200 21/28-Day dermal toxicity in rabbits	41069101 (1988) Acceptable 0, 0.05, 0.5 or 5.0 mg/kg/day	NOAEL = 0.05 mg/kg/day LOAEL = 0.5 mg/kg/day based on edema and erythema and necrosis, edema and erythema at 5.0 mg/kg/day. There was no systemic toxicity.
870.3700a Prenatal developmental in rats	00072693 (1980) Acceptable 0, 15, 30 or 60 mg/kg/day	**Maternal** NOAEL = 15 mg/kg/day LOAEL = 30 mg/kg/day based on body weight decrement. **Developmental** NOAEL = 60 mg/kg/day LOAEL = None based on no developmental effects.
870.3700b Prenatal developmental in rabbits	00079319 (1981) Acceptable 0, 1.0, 5.0 or 10 mg/kg/day	**Maternal** NOAEL = 1.0 mg/kg/day LOAEL = 5.0 mg/kg/day based on stomach lesions, anorexia, abortions and death. **Developmental** NOAEL = 5.0 mg/kg/day LOAEL = 10 mg/kg/day based on total litter resorptions and post implantation loss.
870.3700c Prenatal developmental in rabbits	00049230 and 00069880 Unacceptable 0, 3 or 10 mg/kg/day	**Maternal** NOAEL = 10 mg/kg/day LOAEL = None based on no effects. **Developmental** NOAEL = 10 mg/kg/day LOAEL = None based on no effects.
870.3800 Reproduction and fertility effects in rats	41540601 (1990) Acceptable 0, 40, 75, 250 or 500 ppm M: 0, 2.4, 4.5, 14.8 or 30 mg/kg/day F: 0, 2.8, 5.1, 16.6 or 33.6 mg/kg/day	**Parental/Systemic** NOAEL = 14.8 mg/kg/day LOAEL = 30 mg/kg/day based on male body weight decrement. **Reproductive** NOAEL = 30 mg/kg/day LOAEL = None based on no effects on fertility. **Offspring** NOAEL = 5.1 mg/kg/day LOAEL = 16.6 mg/kg/day based on pup weight decrement on lactational days 0-4, 14 and 21 for females.
870.4100a Chronic toxicity in rats	00067049 (1973) Acceptable 0, 50, 100, 300 or 600 ppm 0, 2.5, 5, 15 or 30 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on elevated alkaline phosphatase. **No evidence of carcinogenicity**

Table 2. Subchronic, Chronic, Mutagenicity and Other Toxicity of Fenbutatin-oxide.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity dogs	00037583 (1973) Unacceptable 0, 2.5, 5.0, 15, 30 or 60 mg/kg/day	NOAEL = not determinable LOAEL = not determinable
870.4300 Carcinogenicity mice	00037581(1973) Acceptable 0, 50, 100, 300 or 600 ppm 0, 7.5, 15, 45, 90 mg/kg/day	NOAEL = 15 mg/kg/day LOAEL = 45 mg/kg/day based on body weight decrement and a nominal decrease in food efficiency. **No evidence of carcinogenicity**
Gene mutation 870.5100; Reverse mutation in Salmonella strains	40473502 and 40770601 (1985) Acceptable	No evidence of mutagenic potential with and without activation at cytotoxic doses.
Gene mutation 870.5300; CHO/HPRT assay	40590504 (1988) Acceptable	No evidence of mutagenic potential with and without activation at cytotoxic doses.
Cytogenics 870.5375; Chromosomal aberrations in human lymphocytes	40590502 (1988) Acceptable	No evidence of mutagenic potential with and without activation at cytotoxic doses.
Other Effects 870.5550, UDS in rat hepatocytes	40590505 (1988) Acceptable	No evidence of mutagenic potential at cytotoxic doses.
Other Effects 870.5385, Mouse bone marrow micronucleus test	40590503 (1988) Acceptable	No evidence of mutagenic potential; not clastogenic at toxic dose levels.
870.7485 Metabolism and pharmacokinetics	41069101 (1989) Acceptable	No accumulation. Less than 1% is excreted in the urine with the remaining being excreted in feces. Insignificant metabolic products were seen. No significant change in metabolism between 10 mg/kg dose and 500 mg/kg dose.
870.7600 Dermal penetration	Not conducted	-

3.2 FQPA Considerations

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on April 22, 2002 to reevaluate the hazard and exposure data for fenbutatin-oxide with regard to making a decision on the additional safety factor for the protection of infants and children. The SFC determined that reliable data demonstrate that the safety of infants and children will be protected by use of an additional safety factor of 3X based on the following:

1. FQPA Safety Factor Recommendations

The FQPA SFC recommends that OPP depart from the default 10X additional safety factor and instead use a different additional safety factor of 3X. This recommendation is based on reliable data supporting the findings set forth below.

A. Traditional Additional Safety Factor (Addressing Data Deficiencies)

Based on the HIARC recommendation, the FQPA SFC recommends use of a 3X additional safety factor to address the data deficiency for a subchronic neurotoxicity study. The rationale for why reliable data support the safety of using a 3X to address this data deficiency follows:

The subchronic neurotoxicity study in rats is identified as a data gap based on the evidence that at 600 ppm (30 mg/kg/day) male absolute brain weight was significantly reduced (3%) at termination in a 90-day feeding study in rats and by the same amount at the 24 month sacrifice in the chronic/carcinogenicity study in rats. The HIARC concluded that an additional database safety factor of 3X is required due to the absence of this study. An uncertainty factor of 3X (as opposed to a higher value) was deemed to be adequate because: 1) the absolute brain weights were decreased only at the highest dose level tested (30 mg/kg/day); 2) the brain weight decreases were only seen in males; 3) the brain weights were decreased at a dose level that is six times higher (30 mg/kg/day) than that used in establishing toxicity endpoints for all risk assessment scenarios (the offspring NOAEL of 5.1 mg/kg/day in the 2-generation reproduction study in rats); 4) although lower molecular weight alkylorganotins are generally considered neurotoxicants, fenbutatin-oxide is not an alkylorganotin and is a large molecular weight molecule which is absorbed to a much lesser degree (the metabolism study in rats shows that absorption through the gut is less than 1%) than the neurotoxic organotins; and 5) there is no evidence of neuropathy or other neurotoxicity in any of the acute, subchronic or chronic/oncogenicity studies submitted.. Upon receipt and evaluation of the data from the subchronic neurotoxicity study, the need for a developmental neurotoxicity study will be reevaluated.

B. Special FQPA Safety Factors

Taking into account the HIARC recommendation regarding the data deficiency, the FQPA SFC recommends that no Special FQPA Safety Factor is necessary to protect the safety of infants and children in assessing fenbutatin-oxide exposure and risks.

2. Rationale and Findings Regarding Recommendation on Special FQPA Safety Factor

The Committee concluded that no Special FQPA safety factor was needed because:

The toxicology database for fenbutatin-oxide contains acceptable guideline developmental and reproduction studies and there is no quantitative or qualitative evidence of increased susceptibility in rat or rabbit fetuses following *in utero* in the standard prenatal developmental studies. Although there is quantitative evidence increased susceptibility in the 2-generation reproduction study in rats, HIARC concluded there is a low degree of concern (and no residual uncertainties) for the effects seen in this study. In determining the degree of concern for these findings in the reproduction study, HIARC considered the overall quality of the study; the dose levels at which the pup effects were observed; and the comparative severity of the effects. The HIARC concluded that there is low concern (and no residual uncertainties) for the susceptibility since: 1) the study was well conducted; 2) the dose response in offspring is well characterized; 3) clear NOAEL and LOAEL were established for the effects on the offspring; 4) the dose spacing is appropriate; 5) the effects observed in pups and parents were qualitatively comparable (body weight loss); and 6) the NOAEL for pup effects was used in establishing the toxicity endpoints for all risk assessment scenarios. The RfDs and toxicity endpoint established are protective of pre-pre/postnatal toxicity following acute and chronic exposures.

There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessment includes anticipated residues calculated from monitoring and field trial data, percent crop treated information (as applicable), and processing data. The dietary drinking water assessment includes a complete environmental fate database and uses modeling results based on chemical-specific data. These assessments will not underestimate the exposure and risks posed by fenbutatin-oxide.

3. Application of the FQPA Safety Factors (Population Subgroups / Risk Assessment Scenarios)

The FQPA safety factor recommendation is for a 3x database uncertainty safety factor to address data deficiencies and no additional Special FQPA safety factor. The 3x safety factor should be applied to all dietary and residential nondietary exposure scenarios. No other FQPA safety factor would be appropriate for fenbutatin-oxide.

3.3 Dose Response Assessment

On August 23, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) selected doses and toxicological endpoints for use in dietary and occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to fenbutatin-oxide was also evaluated as required by the Food Quality Protection act (FQPA) of 1996. On April 4, 2002, HED's HIARC reviewed the Griffin L.L.C. Phase 1 Error Correction comments on the Preliminary Human Health Risk Assessment document for fenbutatin-oxide and re-evaluated the hazard assessment according to the 2002 OPP 10X Guidance Document. A summary of the doses and toxicological endpoints for use in risk assessment is given in Table 3. Also included in this table is the FQPA Safety Factor (SF) selected by the FQPA Safety Factor Committee on April 22, 2002. This table is followed by rationales for the selection of endpoints and doses.

Table 3. Summary of Toxicological Dose and Endpoints for FENBUTATIN-OXIDE for Use in Human Risk Assessment

Exposure Scenario	DOSE (mg/kg/day) UF/MOE[a]	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute Dietary (females 13-50)	None		An appropriate endpoint attributable to a single dose was not identified
Acute Dietary general population including infants and children	None		An appropriate endpoint attributable to a single dose was not identified
Chronic Dietary	NOAEL=5.1 UF = 300 Chronic RfD = 0.017 mg/kg/day	1X	Two Generation Reproduction/rat LOAEL=16.6 mg/kg/day based on F2 pup weight gain decrement between lactational day 0-4 and F2 pup weigh decrement during the remaining lactational period.
Non-Dietary Risk Assessments			
Incidental Oral, Short- and Intermediate-Term Residential only	NOAEL= 5.1 MOE = 300	1X	Two Generation Reproduction/rat LOAEL=16.6 mg/kg/day based on F2 pup weight gain decrement between lactational day 0-4 and F2 pup weigh decrement during the remaining lactational period.
Dermal, Short-, Intermediate- and Long-Term	Oral NOAEL[b]= 5.1		Two Generation Reproduction/rat LOAEL=16.6 mg/kg/day based on F2 pup weight gain decrement between lactational day 0-4 and F2 pup weigh decrement during the remaining lactational period.
Residential only	MOE = 300	1X	
Occupational	MOE = 100	N/A	
Inhalation, Short-, Intermediate-and Long-Term	Oral NOAEL[c]= 5.1		Two Generation Reproduction/rat LOAEL=16.6 mg/kg/day based on F2 pup weight gain decrement between lactational day 0-4 and F2 pup weigh decrement during the remaining lactational period.
Residential	MOE = 300	1X	
Occupational	MOE = 100	N/A	
Cancer (oral, dermal, inhalation)	Cancer classification group E; not likely to be a human carcinogen	N/A	No neoplastic lesions in rats or mice.

a = 300 (10x for interspecies extrapolation and 10x for intraspecies variations and 3x for a FQPA UF_{DB} data gap)
b = Use 10% dermal absorption factor for route-to-route extrapolation
c = Absorption via inhalation is assumed to be equivalent to oral absorption.

Acute Reference Dose (RfD)
No appropriate endpoint was available to quantitate risk to the general U.S. population or to females 13-50 years old from a single-dose administration of fenbutatin-oxide.

Chronic Reference Dose (RfD)
A chronic/carcinogenicity study in rats with a NOAEL/LOAEL = 5/15 mg/kg/day supports the NOAEL from the study on reproduction. The HIARC noted the lack of a chronic toxicity study in dogs; however, the committee did not apply an additional uncertainty factor for the data gap, since the toxicological profile of this chemical indicated that a study in dogs is unlikely to yield a lower NOAEL than the one used for deriving the RfD.

Short- and Intermediate-term Incidental Oral Exposure
The NOAEL is 5.1 mg/kg/day for offspring based on decreased F2 male and female pup body weight gain during lactation at a LOAEL of 16.6 mg/kg/day. The pup weight gain decreases occurred during lactation but did not occur at birth. There was a 19% decrement in F2 pup weight gain between lactational day 0 and day 4 and a 11% pup weight gain decrement between lactational day 0 and day 20. Thus, the effects seen during this time period (i.e., lactational days 0-20 is appropriate for both short-term (1-30 days) and intermediate-term (30 days to 6 months) exposure durations and the population of concern (toddlers).

Short-, Intermediate-, and Long-term Dermal Exposure
The NOAEL is 5.1 mg/kg/day for offspring based on decreased F2 male and female pup body weight gain during lactation at a LOAEL of 16.6 mg/kg/day. The pup weight gain decreases occurred during lactation but did not occur at birth. There was a 19% decrement in F2 pup weight gain between lactational day 0 and day 4 and a 11% pup weight gain decrement between lactational day 0 and day 21. In the absence of systemic dermal toxicity, this oral endpoint, which is protective of offspring/reproductive effects, was selected. A 10% dermal absorption factor was used for route-to-route extrapolation.

Short-, Intermediate-, and Long-term Inhalation Exposure
The NOAEL is 5.1 mg/kg/day for offspring based on decreased F2 male and female pup body weight gain during lactation at a LOAEL of 16.6 mg/kg/day. In the absence of an inhalation study, an oral NOAEL was selected. This dose/endpoint was also used for the dermal risk assessments for the same time periods, and would be protective of offspring/reproductive effects.

3.4 Endocrine Disruption

There is no evidence that fenbutatin-oxide induces any endocrine disruption. EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may

designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

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

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Uses

Fenbutatin-oxide is an organotin acaricide effective against mites on almonds, apples, cherries, citrus fruits, eggplant, grapes, papayas, peaches, pears, pecans, plums, raspberries, strawberries, and walnuts, greenhouse crops, and ornamentals. Based on a search of OPP's REFS conducted on 24-August-2001, there are three active Section 3 registrations for end-use products containing fenbutatin-oxide. One product is a Restricted Use wettable powder (WP; 50% ai) registered for use on terrestrial food/non-food crops and greenhouse food/non-food crops which may only be applied by a Certified Applicator. This 50% WP is marketed in 1 lb water-soluble packs and may be applied up to four times/year foliarly using ground boom, air blast or aerial equipment. The other two end-use products are emulsifiable concentrates (EC; 0.5 and 0.75 ai) which are marketed for non-occupational uses in residential settings on ornamentals. These products are sold in pint or quart size containers and are typically applied up to six times/year using handheld equipment.

From sales information provided by Griffin L.L.C. at the SMART meeting with EPA on 21-June-2001, 96% and 4% of the total lb ai fenbutatin-oxide is used on agricultural and non-agricultural use sites, respectively. The key market locations are Florida and California and the crop receiving the greatest allocation is citrus (50% total lb ai). A summary of the currently registered end-use products and use sites is given in the table below:

Company	EPA Reg. No.	Formulation Class	% ai	Use Sites
The Scotts Co.	239-2594	EC	0.75	Roses, Flowers, Shrubs and Shade Trees
The Scotts Co.	239-2595	EC	0.50	Roses, Flowers, Trees, Shrubs
Griffin L.L.C.	1812-413	WP	50	*Food/Feeds:* Almonds, Apples, Cherries (sweet/sour), Citrus, Eggplant, Grapes, Nectarines, Papayas, Peaches, Pears, Pecans, Plums, Prunes, Raspberries, Strawberries, Walnuts *Non-Food:* Christmas trees, Greenhouse and Outdoor Ornamentals, Established Landscape Ornamentals

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Tolerances for residues of fenbutatin-oxide in or on food/feed commodities are currently expressed in terms of the combined residues of hexakis(2-methyl-2-phenylpropyl)-distannoxane and its organotin metabolites calculated as hexakis(2-methyl-2-phenylpropyl)-distannoxane [listed in 40 CFR §180.362 (a), (b) and (c)].

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for residues of fenbutatin oxide in/on various commodities. The Codex MRLs (currently expressed in terms of fenbutatin oxide per se) and applicable U.S. tolerances (currently expressed in terms of the combined residues of fenbutatin oxide and its organotin metabolites) are incompatible. HED has recommended that the tolerance expression for plants should include fenbutatin-oxide only and for meat, milk, poultry and eggs the tolerance expression should include metabolites dihydroxybis(2-methyl-2-phenylpropyl)stannane (SD-31723) and 2-methyl-2-phenylpropyl-stannoic acid (SD-33608) as well as the parent. Because of the differences between the Codex and the current and recommended U.S. tolerance expressions for animal commodities, compatibility is not achievable.

The HED Metabolism Committee (27-January-1993) has concluded that the toxic residues resulting from use of fenbutatin-oxide are the parent compound and its organotin metabolites dihydroxybis(2-methyl-2-phenylpropyl)stannane (SD-31723) and 2-methyl-2-phenylpropyl-stannoic acid (SD-33608). The Committee further recommended that the tolerance expression for plants should include fenbutatin-oxide only and for meat, milk, poultry and eggs the tolerance expression should include metabolites dihydroxybis(2-methyl-2-phenylpropyl)stannane (SD-31723) and 2-methyl-2-phenylpropyl-stannoic acid (SD-33608) as well as the parent.

Although parent fenbutatin-oxide and its organotin metabolites are of toxicological concern in both plants and animals, HED has concluded that for plants the parent compound only should be included in the dietary risk assessment. Metabolism studies with apples and oranges indicate that parent material comprises the majority (44-86%) of the terminal residue in these plants; SD31723 accounted for less than 10% of the total toxic residues (TTR). For meat and milk, the risk assessment should include the parent compound and its organotin metabolites dihydroxybis(2-methyl-2-phenylpropyl)stannane (SD-31723) and 2-methyl-2-phenylpropyl-stannoic acid (SD-33608).

GLN 860.1300: Nature of the Residue- Plant

Metabolism studies with apples and oranges provide an adequate understanding of the nature of the residue in plants to support the currently registered food/feed uses. These data indicate that residues in/on fruit are primarily surface residues and that parent material was the predominant compound. Results indicated treated apples (31 and 60 days after 2 doses) contained (0.02 mg and 0.04 mg of ^{119}Sn-hexakis) 77-86% parent, 3-4% SD31723, 0.6% other organic compounds, and 7-9% inorganic compounds. For orange peels (after 2 treatments, 0.132-0.2 ppm) contained 44-65% parent, 4.5-7% SD31723 and 2-3% inorganic tin. HED has concluded that for plants, the parent compound only should be included in the risk assessment. In the plant metabolism studies for apples and oranges, the parent compound was the predominant compound in plants. Since the parent compound comprises the majority of the terminal residue in plants, only the parent will be included in the tolerance expression for plant commodities (MARC memo, L.Cheng, 1/27/93).

Should additional crops be added to the label, additional metabolism data may be required.

GLN 860.1300: Nature of the Residue- Animals

Metabolism studies in goats and poultry provide an adequate understanding of the nature of the residue in livestock to support the currently registered food/feed uses. Fenbutatin-oxide and its metabolites did not bioaccumulate in milk, meat and fat of cattle dosed at 34 ppm ^{119}Sn-hexakis (0.5x of the maximum dietary burden). In kidney and liver of cattle, hexakis and SD31723 accounted for 50-70% TRR and inorganic tin residues accounted for 30-50% of the terminal residues. Studies with goats and poultry revealed similar metabolic profiles. The terminal residue to be regulated in livestock consists of fenbutatin oxide and its metabolites SD-31723 and SD-33608 (MARC memo, L.Cheng, 1/27/93).

GLN 860.1340: Residue Analytical Methods - Plants and Animals:

An adequate enforcement method is available for fenbutatin oxide residues in plants and animals. The GLC/FPD method MMS-R-494-2 has undergone successful Agency method validation for plants and animals and has satisfied the requirements of PR Notice 88-5 concerning independent

laboratory validation. Method MMS-R-494-2 individually quantifies each analyte to a detection limit of 0.05 ppm. It has been forwarded to FDA for inclusion in PAM, Vol. II as Method III.

4.2.2 Acute Dietary

Review of all available fenbutatin-oxide toxicity data did not identify an appropriate endpoint attributable to a single oral dose for either the general U.S. population (including infants and children) or the females 13-50 years old population subgroup. Therefore, an acute dietary exposure analysis was not performed.

4.2.3 Chronic Dietary

A Tier 3 chronic dietary exposure assessment was conducted for fenbutatin-oxide using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.73, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992.

Anticipated residues (ARs) from USDA's Pesticide Data Program (PDP) and field trial data were utilized to estimate the dietary exposure to the general U.S. population and certain population subgroups. Monitoring data from PDP (1995-96 and 1998) were used for apples, grapes, oranges peaches, and pears. PDP data for oranges were translated to grapefruit, lemons, limes, tangelos, and tangerines. FDA monitoring data are not available. If a commodity had no reported detections in the field trial data, half the limit of detection (LOD) was used to account for possible exposure that could not be more precisely quantified. For purposes of this assessment, the LOD for fenbutatin-oxide is assumed to be 0.003 ppm. The weighted average estimate of % crop treated (J. Alsadek, BEAD, 09/20/01) and processing information for apples and oranges were incorporated into this assessment. The calculated chronic dietary exposure (residue x consumption) was compared to a cPAD of 0.017 mg/kg/day, which reflects a FQPA factor of 10X for the U.S. population and all population subgroups.

As shown in Table 4, the chronic dietary risk estimates associated with the use of fenbutatin-oxide do not exceed HED's level of concern (≥100%) for any population subgroup. The chronic dietary exposure estimate for all infants <1 year of age (the highest exposed population subgroup) is 1.0% of the cPAD. The chronic significant contributor was identified as plums/prunes.

Table 4: Chronic Dietary Risk Estimates		
Population	**Exposure mg/kg/day**	**% Chronic PAD**
U.S. Population	0.000041	<1
All Infants (<1 year)	**0.000169**	**1.0**
Children 1-6 years	0.000089	<1
Children 7-12 years	0.000045	<1
Females 13-50 years	0.000031	<1
Males 13-19 years	0.000013	<1
Males 20+ years	0.000029	<1
Seniors 55+ years	0.000051	<1

No poultry or swine feed items are associated with the registered uses; therefore, there is no reasonable expectation of detectable residues of fenbutatin-oxide and its organotin metabolites in poultry, swine and eggs resulting from use patterns being considered for reregistration. These uses for poultry, swine and eggs can be classified under Category 3 of 40 CFR 180.6(a).

Characterization/Uncertainties of the Chronic Dietary Risk Estimate:
Fenbutatin-oxide residue estimates, or ARs used in this chronic dietary exposure assessment are based primarily on field trial data, submitted by the registrant to support tolerances. Field trial residue data are generally considered by HED as an upper-end or a worse case scenario of possible residues and are more suited to the requirements of tolerance setting, because it requires highest rates of application and shortest preharvest interval (PHI), than to the requirements of dietary exposure assessment (when the most realistic estimate is desired). It is further noted that cucumbers were included in the dietary exposure estimates because a tolerance for residues on this commodity is currently listed under 40 CFR 180.362(a); however, use of fenbutatin-oxide on this site is not listed on current product labels and is not being supported for reregistration.

The Agency notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups from the general U.S. population which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, dietary risks estimated for these population subgroups were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

4.2.4 Cancer Dietary

Fenbutatin-oxide has been placed in group E; no evidence of carcinogenicity in the rat or mouse. Therefore, a dietary exposure assessment for cancer risk is not required for fenbutatin-oxide.

4.3 Water Exposure/Risk Pathway

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis and risk assessment for fenbutatin-oxide. Therefore, the Agency is presently relying on computer-generated estimated environmental concentrations (EECs). GENEEC and/or PRZM/EXAMS are used to generate EECs for *surface* water and SCI-GROW (an empirical model based upon actual monitoring data collected for a number of pesticides that serve as benchmarks) predicts EECs in *ground* water. These models take into account the use patterns and the environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a screen for determining whether pesticide residues (and metabolites) in water are not of concern.

The Environmental Fate and Effects Division (L. Shananman, 31-July-2001) provided the drinking water assessment using simulation models to estimate the potential concentration of fenbutatin-oxide in ground and surface water. Monitoring data are not available for fenbutatin-oxide. There is no Maximum Contaminant Level Goal (MCLG) or Maximum Contaminant Level (MCL) established by the Agency's Office of Water for fenbutatin-oxide.

Environmental Profile: The environmental fate database is complete for fenbutatin-oxide. Available data indicate that fenbutatin-oxide is persistent but very immobile. While laboratory data indicate that fenbutatin-oxide is expected to be persistent in the environment, studies also indicate that fenbutatin-oxide undergoes an extremely strong binding to soils. This propensity towards binding precludes the possibility of significant concentrations being present in surface waters, and mitigates any potential to accumulate in ground waters.

MARC Decision: The HED Metabolism Assessment Review Committee concluded that the residue of concern for drinking water risk assessment is fenbutatin-oxide *per se.*

Estimated Environmental Concentrations:
Tier II (PRZM/EXAMS) surface water modeling for fenbutatin-oxide residues using the index reservoir with the percent cropped area, predicts the 1 in 10 year peak (acute) concentration of fenbutatin-oxide residues is not likely to exceed 18.5 µg/L. The 1 in 10 year annual average concentration (non-cancer chronic) of fenbutatin-oxide residues is not likely to exceed 6.0 µg/L. The SCI-GROW predicted concentration of fenbutatin-oxide in ground water is not expected to exceed 0.0060 µg/L.

Assumptions/Uncertainties for Water Exposure Pathway:
These EEC concentrations were predicted from recommended use information for citrus crops in Florida. Although slightly higher use rates (3 lb ai/A vs. 2 lb ai/A) are allowed for the use of fenbutatin-oxide on Arizona, California and Texas citrus, the standard Florida citrus scenario was chosen to model EECs as this scenario can adequately represent upper-bound estimates of the concentrations that might be found in surface water and ground water because: 1) the soil modeled in Florida is more vulnerable to runoff than would be expected in Texas; and 2) Florida meteorological conditions (high rainfall) are expected to result in higher pesticide runoff than would occur under dryer conditions in Texas.

Characterization: Fenbutatin-oxide is labeled for use predominantly on orchard crops, with eggplant and strawberries being the exceptions. The normal use of ground cover in orchards would inhibit significant amounts of soil being carried into water bodies by erosion. Additionally, once fenbutatin oxide has come in contact with the soil, it is unlikely to desorb back into water. Although it is possible for fenbutatin oxide to move to neighboring water bodies with a major rain event occurring shortly after application, initial concentrations are expected to be very low, followed by fenbutatin-oxide partitioning quickly and persistently to sediment.

4.4 Residential Exposure/Risk Pathway

4.4.1 Residential/Recreational Use Pattern

Fenbutatin-oxide is a miticide/acaricide used in commercial/residential settings for control of mites and diseases on ornamental plants, including roses, flowers, shrubs and trees. Fenbutatin-oxide is formulated as a Restricted Use wettable powder (50 percent ai) for occupational application to commercial/residential sites by only Certified Applicators, and as an emulsifiable concentrate liquid (0.5 to 0.75 percent ai) for non-occupational application to residential sites. The non-occupational home and garden end-use products also contain the active ingredient, acephate. The risk potential for exposure to acephate in these products has been addressed in the acephate risk assessment.

4.4.1.1 Non-Occupational Handler Exposure

Non-occupational (residential) use of fenbutatin-oxide products may result in dermal and inhalation exposure to adult handlers. Fenbutatin-oxide is applied to residential ornamentals at a maximum application rate of 0.0005 lbs ai/gallon using the following equipment: 1) low pressure handwand; 2) backpack sprayer; and 3) hose-end sprayer. The fenbutatin-oxide homeowner products are typically applied post-emergent up to six times per year with four week intervals between applications. The duration of exposure for residential populations is assumed to be short-term (1-30 days) only because application for pest control occurs about once a month during the growing season of approximately six months.

4.4.1.2 Handler Exposure Data Sources/Assumptions

No chemical specific handler exposure data are available for fenbutatin-oxide. The exposure assessments for the scenarios (1) low pressure handwand and (3) hose-end sprayer were developed using handler exposure data submitted by the Outdoor Residential Exposure Task Force (ORETF). The exposure assessment for scenario (2) backpack sprayer was developed using the Pesticide Handlers Exposure Database (PHED) Version 1.1. Table 5 summaries the caveats and parameters specific to the surrogate data used for each scenario and corresponding exposure/risk assessment.

The following assumptions were made in the exposure calculations:

- Average body weight of an adult handler is 60 kg because the endpoint for risk assessment is based on offspring effects from a rat-reproduction study.

- Generally, the use of personal protective equipment (PPE) and engineering controls are not considered acceptable options for products sold for use by homeowners, because they are not available and/or are inappropriate for the exposure scenario.

- Calculations are completed at the maximum application rates for ornamental use sites as stated on the available fenbutatin-oxide labels.

Table 5. Residential Handler Exposure Scenario Descriptions for Fenbutatin-oxide.

Exposure Scenario (Number)	Data Source[a]	Comments[b]	Standard Assumption[c]
Mixer/Loader/Applicator Descriptors			
Mixing/Loading/Applying Liquids with a Low Pressure Handwand (1)	Outdoor Residential Exposure Task Force (ORETF) Chemical Handler Exposure Studies	**Baseline:** Dermal, inhalation, and hands = A grade. Dermal, inhalation, and hands = 20 replicates each. High confidence in all data. *PPE and Engineering Controls: Not* required for assessment.	5 gallons/day
Mixing/Loading/Applying Using a Backpack Sprayer (2)	PHED V1.1	**Baseline:** Dermal = AB grade; inhalation = A grade; and hands = C grade. Dermal = 9 to 11 replicates; hands = 11 replicates; and inhalation = 11 replicates. Low confidence in dermal, and inhalation data. A 90% protection factor was used to back calculate "no glove" hand data from the gloved scenario. PPE and Engineering Controls: Not required for assessment.	5 gallons/day
Mixing/Loading/Applying Using a Garden Hose-end Sprayer (3)	ORETF Chemical Handler Exposure Studies	**Baseline:** Dermal, inhalation, and hands = A grade. Dermal, inhalation, and hands = 20 replicates each. High confidence in all data. PPE and Engineering Controls: Not required for assessment.	32 gallons/day

[a] The Scotts Company is a member of the ORETF and data compensation is not an issue.

[b] "Best Available" grades are defined by HED SOP for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates

[c] Standard Assumptions taken from HED Exposure SAC Policy No. 12.

4.4.1.3 Handler Risk Characterization

Risks were calculated using the Margin of Exposure (MOE) approach, which is a ratio of exposure to the toxicological endpoint of concern. Decreased body weight gain in F2 offspring was selected as the toxicity endpoint for short-term dermal and inhalation risk assessment. The MOEs derived for short-term exposure were based upon comparison of dermal and inhalation exposure estimates against a NOAEL of 5.1 mg/kg/day from an oral reproduction toxicity study in the rat. The risk calculations incorporated a 10% dermal absorption factor and a 100% inhalation absorption factor for dermal and inhalation exposures, respectively. An uncertainty factor (UF) of 100 was applied to the dose selected for risk assessment to account for both interspecies extrapolation and intraspecies variability. The FQPA SFC recommended that a 3X database uncertainty safety factor to address data deficiencies and no additional Special FQPA safety factor be applied to all residential nondietary exposure scenarios. An MOE ≥300 does not present a risk concern for residential handlers.

Table 6 presents the findings for all residential handler scenarios. Calculations based on combined dermal and inhalation risk indicate that the total MOEs are greater than 300 (the lowest MOE was 4,900) when fenbutatin-oxide is applied using a low-pressure handwand, a backpack sprayer, or a hose-end sprayer.

Characterization/Uncertainties of the Residential Risk Estimate:
High confidence data were used to develop dermal and inhalation exposure estimates for application using a garden hose-end sprayer and low confidence data were used to calculate the risks to handlers from the use of backpack application equipment.

The extent to which fenbutatin-oxide is absorbed following dermal exposure is not well characterized. The potential for dermal absorption is believed to be very low based on the physiochemical properties of fenbutatin-oxide; however, no studies are available to directly provide a dermal absorption factor. An upperbound dermal absorption factor was determined to be 10% based on a comparison of the physical-chemical characteristics of fenbutatin-oxide and triphenyltin-hydroxide (TPTH). Although the dermal absorption of fenbutatin-oxide is believed to be less than 10%, there is insufficient data to support a smaller factor.

Table 6. Residential Handler Short-term Dermal and Inhalation Exposure to Fenbutatin-oxide at Baseline.

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[a]	Inhalation Unit Exposure (μg/lb ai)[b]	Application Rate (lbs ai/gal of spray)[c]	Amount Used per Day[d] (gallons)	Daily Dermal Dose (mg/day/kg)[e]	Daily Inhalation Dose (mg/day/day)[f]	Dermal MOE[g]	Inhalation MOE[h]	Total MOE[i]
MIXER/LOADER/APPLICATOR EXPOSURE									
Mixing/Loading/Applying Liquids with Low Pressure Hand Wand (1)	56	4.3	0.0005	5	0.00023	0.0000002	22,000	2.8[7]	22,000
Mixing/Loading/Applying Liquids with Backpack Sprayer (2)	5.1	30	0.0005	5	0.000021	0.0000013	240,000	4.1[6]	230,000
Mixing/Loading/Applying Liquids with Hose-end Sprayer (3)	39	2.6	0.0005	32	0.00104	0.0000007	4,900	7.4[6]	4,900

Footnotes:

a Dermal unit exposure represents short pants, short-sleeved shirt, no gloves, open mixing/loading.

b Inhalation unit exposure represents no respirator.

c Application Rates are based on the maximum application rates listed on the fenbutatin-oxide labels.

d Amount used per day are from EPA estimates of gallon used in a single day based on the application method.

e Daily Dermal Dose (mg/kg/day) = (Dermal Unit Exposure (mg/lb ai) x Application Rates (lb ai/gallon spray) x Amount Used per day (gallons)x 10% dermal absorption/ body weight (60 kg).

f Daily Inhalation dose (mg/kg/day) = (Inhalation Unit Exposure (μg/lb ai) x (1 mg/1000 μg) Conversion Factor x Application Rate (lb ai/gallon spray) x Amount Used per day (gallons))/ body weight (60 kg).

g Short-term Dermal MOE = Dermal NOAEL (5.1 mg/kg/day)/ Daily Dermal Dose (mg/kg/day).

h Short-term Inhalation MOE = Inhalation NOAEL (5.1 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).

i Total MOE = 1/(1/dermal MOE + 1/inhalation MOE). Target MOE = 300.

4.4.2 Non-Occupational Postapplication Exposure

Fenbutatin-oxide can be used on ornamentals in residential and non-occupational settings such as parks and other recreational areas. However, HED has determined that no significant post-application exposure to adults or children in residential settings is anticipated from spot treating ornamentals; therefore, no post-application scenarios are being assessed.

4.4.3 Other Non-Occupational Exposure

This assessment for fenbutatin-oxide reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999, meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources not addressed such as from spray drift; residential residue track-in; exposures to farmworker children; and exposures to children in schools.

4.4.4 Incidents Reports

The following data bases were consulted for the poisoning incident data on fenbutatin-oxide:

- OPP Incident Data System (IDS) - 1992 to present;
- Poison Control Centers (PCC) - 1993 to 1998;
- California Department of Pesticide Regulation - 1982 to 1999; and
- National Pesticide Telecommunications Network (NPTN) -1984 to1991.[2]

The IDS reported 440 incidents involving products containing fenbutatin-oxide and another active ingredient, most commonly the organophosphate, acephate. It is not possible to distinguish in these cases whether symptoms resulted from the exposure to acephate or fenbutatin-oxide. Therefore, no attempt is made to recount any of these incidents. The PCC reported only seven incidents of exposure to products containing just fenbutatin-oxide. Four of the seven cases involved occupational exposure and none of the cases experienced or were expected to experience more than a minor medical outcome. The California Department of Pesticide Regulation reported 80 incidents involving fenbutatin-oxide, but fenbutatin-oxide was judged to be responsible for the health effects in only eight of the cases. NPTN reported 19 incidents in humans and three incidents in animals (mostly pets). In conclusion, very few illness cases have been reported due to fenbutatin-oxide and none have been confirmed. Therefore, no recommendations can be made on the very limited incident data available.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATIONS

An aggregate exposure risk assessment was performed for two exposure durations: short-term (residential + average food/water) and chronic (food + drinking water). Acute and cancer aggregate risk assessments were not performed; an acute dietary endpoint was not selected and fenbutatin-oxide is not carcinogenic. Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate the chronic DWLOCs, the chronic dietary exposure estimates from food (from DEEM™) were subtracted from the cPAD value to obtain the allowable average exposure to fenbutatin-oxide in drinking water. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (adult male and U.S. Population), 60 kg/2L (adult female), and 10kg/1L (infant & children).

DWLOCs are compared to EECs for a pesticide in surface water and ground water. If the DWLOCs are greater than the EECs, HED concludes with reasonable certainty that estimates of aggregate risks are below HED's level of concern.

5.1 Acute Aggregate Risk

An appropriate endpoint attributable to a single oral dose was not identified in any fenbutatin-oxide study including the rat and rabbit developmental toxicity studies; therefore, it is not necessary to conduct an acute aggregate dietary (food and water) risk analysis.

5.2 Short-Term Risk

5.2.1 Aggregate Short-Term Risk Assessment

Short-term aggregate exposure takes into account residential exposure plus average (chronic) exposure to food and water (considered to be a background exposure level). Fenbutatin-oxide is currently registered for uses that could result in short-term residential handler exposure. HED has determined that, based on the short-term, non-dietary toxicity profile, it is appropriate to aggregate food, water, and residential pathways of exposure for assessment of short-term risks.

5.2.2 Aggregate Short-Term DWLOC Calculations

In determining short-term aggregate risks, HED selected the residential handler exposure scenario resulting in the highest total exposure potential, mixing/loading/applying liquids with a hose-end sprayer. Total dermal and inhalation exposures for this scenario were combined with average food exposures to calculate short-term aggregate MOEs and DWLOCs.

As shown in Table 7, the EEC values used for comparison to the short-term DWLOC are 6 ppb (surface water) and 0.006 ppb (ground water). These estimated environmental concentrations are less than 468 ppb which is HED's lowest drinking water level of comparison for exposure to fenbutatin-oxide in drinking water as a contribution to aggregate short-term risk. For all populations assessed, the DWLOCs are greater than the average ground water EECs; therefore, aggregate short-term exposure to fenbutatin-oxide is not expected to exceed HED's level of concern.

Table 7. Short-Term Aggregate Risk and DWLOC Calculations

Population	*Short or Intermediate*-Term Scenario									
	NOAEL mg/kg/day	Target MOE[1]	Max Exposure[2] mg/kg/day	Average Food Exposure mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate MOE (food and residential)[4]	Max Water Exposure[5] mg/kg/day	Ground Water EEC[6] (ppb)	Surface Water EEC[6] (ppb)	Short-Term DWLOC[7] (ppb)
U.S. Population	5	300	0.01667	0.000029	0.00104	4677	0.015598	0.006	6	546
All Infants (<1yr)	N/A									
Children 1-6 years	N/A									
Children 7-12 years	N/A									
Females 13+	5	300	0.01667	0.000031	0.00104	4669	0.015596	0.006	6	468
Males 13-19 years	5	300	0.01667	0.000013	0.00104	4748	0.015614	0.006	6	546
Males 20+ years	5	300	0.01667	0.000029	0.00104	4677	0.015598	0.006	6	546
Seniors 55+ years	5	300	0.01667	0.000051	0.00104	4583	0.015576	0.006	6	545

[1] An uncertainty factor (UF) of 100 was applied to the dose selected for risk assessment to account for both interspecies extrapolation and intraspecies variability. A 3x database uncertainty safety factor to address data deficiencies applies to all dietary and residential nondietary exposure scenarios.

[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE

[3] Residential Exposure = [Dermal exposure (0.00104 mg/kg/d) + Inhalation Exposure (0.0000007 mg/kg/d)]

[4] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]

[5] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)

[6] The crop producing the highest level was used.

[7] DWLOC(μg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/}\mu\text{g]}}$

5.4 Chronic Risk

5.4.1 Aggregate Chronic Risk Assessment

Chronic aggregate risk estimates do not exceed HED's level of concern. The aggregate chronic dietary risk estimates include exposure to residues of fenbutatin-oxide in food and water. No chronic residential use scenarios were identified. Exposure (food only) to residues of fenbutatin-oxide, based on a Tier 3 refinement using USDA/PDP data, average residues from field trials, and percent of crop treated data, represent less than 1.0% of the chronic PAD for the most highly exposed population subgroup (all infants less than 1 year).

5.4.2 Chronic DWLOC Calculations

The EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to fenbutatin-oxide. The EEC values used for comparison to the DWLOC are 6 ppb (surface water) and 0.006 ppb (ground water). These estimated environmental concentrations are less than 168 ppb which is HED's lowest drinking water level of comparison for exposure to fenbutatin-oxide in drinking water as a contribution to aggregate chronic dietary risk. Based on the available information, HED concludes with reasonable certainty that no harm to any population will result from aggregate chronic dietary exposure to fenbutatin-oxide. Details are presented in Table 7.

Table 7. Chronic DWLOC Calculations

Population Subgroup	Chronic Scenario					
	cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[1]	Ground Water EEC (ppb)[2]	Surface Water EEC (ppb)[2]	Chronic DWLOC (μg/L)
U.S. Population	0.017	0.000041	0.016959	0.006	6	594
All Infants (<1yr)	0.017	0.000169	0.016831	0.006	6	168
Children 1-6 years	0.017	0.000089	0.016911	0.006	6	169
Children 7-12 yrs	0.017	0.000045	0.016955	0.006	6	170
Females 13+	0.017	0.000031	0.016969	0.006	6	509
Males 13-19 years	0.017	0.000013	0.016987	0.006	6	595
Males 20+ years	0.017	0.000029	0.016971	0.006	6	594
Seniors 55+ years	0.017	0.000051	0.016949	0.006	6	593

[1]Maximum Chronic Water Exposure (mg/kg/day) = [cPAD (mg/kg/day) - chronic food exposure (mg/kg/day)]
[2]The crop producing the highest level was used.
[3] Chronic DWLOC(μg/L) = [maximum chronic water exposure (mg/kg/day) x body weight (kg)] / [water consumption (L) x 10^{-3} mg/μg]

Table 8. Drinking Water Short-term and Chronic DWLOC and EEC Comparisons				
Population Subgroup	DWLOCs (ppb)		EECs (ppb)	
	Short-Term	Chronic	Ground Water (Acute and Chronic)	Surface Water (Chronic)
U.S. Population	546	594	0.006	6.0
All Infants (<1yr)	N/A	168		
Children 1-6 years	N/A	169		
Children 7-12 yrs	N/A	170		
Females 13+	468	509		
Males 13-19 years	546	595		
Males 20+ years	546	594		
Seniors 55+ years	545	593		

6.0 CUMULATIVE

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

HED did not perform a cumulative risk assessment as part of this tolerance reassessment review for fenbutatin-oxide because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of fenbutatin-oxide. For purposes of this tolerance reassessment review, EPA has assumed that fenbutatin-oxide does not have a common mechanism of toxicity with other substances.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether fenbutatin-oxide shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for fenbutatin-oxide need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with fenbutatin-oxide, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance for conducting cumulative risk assessments is available.

7.0 OCCUPATIONAL EXPOSURE

Because FQPA addresses only non-occupational (residential) risk concerns, risks to occupational workers are not addressed in this document. The Reregistration Eligibility Decision (RED) issued for fenbutatin-oxide in September, 1994 included an occupational exposure and risk assessment as part of the Agency's conclusion that uses of fenbutatin-oxide would not cause unreasonable risk to humans or the environment.

8.0 DATA NEEDS

8.1 Toxicology

- OPPTS 870.3465: 28-Day inhalation toxicity study. The protocol for the existing 90-day inhalation toxicity study should be followed with the exposure (treatment) ending after 28 days, instead of 90 days. The study should be conducted with a 50% formulated product instead of the technical grade of fenbutatin-oxide.

- OPPTS 870.2000: Neurotoxicity Screening Battery

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Chemical:	**Hexakis(2-methyl-2-phenylpropyl)distanno**
PC Code:	**104601**
HED File Code	**14000 Risk Reviews**
Memo Date:	**05/03/2002**
File ID:	***DPD282791***
Accession Number:	**412-02-0282**

HED Records Reference Center
06/04/2002