

State of California

Memorandum

To : Barry Cortez, Chief  
Pesticide Registration Branch

Date : April 28, 1994

Place : Sacramento

Phone: 445-4233

From : Department of Pesticide Regulation - Larry Nelson, Chief  
Medical Toxicology Branch

Subject : Fenoxaprop-ethyl Risk Characterization Document

A risk characterization document for the section 3 registration of the new pesticide active ingredient fenoxaprop-ethyl is forwarded for distribution in accordance with Pest Management Division policy #87-3. Please also provide copies to Both USEPA OPP Special Review and Registration Division and the USEPA OPP Health Effects Division. Prior to distribution, a risk management decision must be obtained from the Director to determine the acceptability of calculated margins of safety and a final registration decision.

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RISK ASSESSMENT OF  
FENOXAPROP-ETHYL

(WHIP®)

VOLUME I  
RISK CHARACTERIZATION DOCUMENT

(4-6-94)

Medical Toxicology Branch

Department of Pesticide Regulation

California Environmental Protection Agency

## EXECUTIVE SUMMARY

Fenoxaprop-ethyl is a herbicide which is selective against perennial and annual grass weeds in many crops. It is a member of the aryloxy phenoxy-propionate class of herbicides, and its mechanism of action is to inhibit fatty acid biosynthesis, in both plant chloroplasts and mammalian liver. The formulation Whip® IEC, is a 12.5% emulsifiable concentrate for which registration is currently being requested in California for use as a postemergence rice herbicide. Whip® has been registered for use in other states since 1987 by the United States Environmental Protection Agency (U.S. EPA). The high potential toxicity of fenoxaprop-ethyl, which was shown in developmental toxicity studies in the rat and monkey, along with possible liver toxicity in longer term studies, was the reason for it entering the risk assessment process. This document addresses the risk from both occupational and dietary exposure to fenoxaprop-ethyl.

### The Risk Assessment Process

The risk assessment process consists of four aspects: hazard identification, dose response assessment, 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 which could potentially cause an adverse effect. The amount which 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 some toxic manifestation. Chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals which require low or high dosages, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies which define the types of toxic effects which 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 toxicity of a pesticide, the other parameters which are critical to determining the risk are the magnitude, frequency and duration of exposure. The purpose of the exposure evaluation is to determine the potential exposure pathways and the amount of pesticide likely to be delivered through those routes. This includes occupational exposure on an acute (short-term), a sub-chronic or a chronic basis. Dietary exposure is also estimated on an acute (daily) and chronic (annual) basis. The level of potential exposure is determined by the amount of pesticide residue on specific commodities and processed foods, and the consumption rate.

The risk characterization then integrates the toxic effects observed in the laboratory studies, conducted with high dosages of pesticide, to potential human exposures from occupational exposure and/or to pesticide residues in the diet. 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 which produced no effects in laboratory studies to the estimated occupational exposure and/or dietary dosage. For oncogenic effects, the probability of risk is calculated as the product of the cancer potency of the pesticide and the estimated exposure dosage.

## **Toxicology**

Based on the currently available data, the Department of Pesticide Regulation has concluded that the principal toxicological effects of fenoxaprop-ethyl probably result from hepatotoxicity. The inhibition of fatty acid biosynthesis, in the liver, may account for the majority of the effects observed. However, increases in liver weight, seen in acute and sub-chronic studies, and decreases in liver weight, which are seen in chronic studies, alone, do not necessarily reflect an adverse effect. This is because liver weight changes have often been found to be reversible, in subchronic studies following the discontinuation of dosing, or through adaptation mechanisms, with the continued dietary intake of fenoxaprop-ethyl, in chronic studies. Developmental toxicity studies showed an increased level of fetal anomalies in the rat and rabbit, as well as maternal mortality of the Cynomolgus monkey. There was no evidence of oncogenicity in the rat, mouse or dog. Similarly, specific effects on (rat) reproduction were not observed.

## **Occupational Exposure**

Estimates of occupational exposure for aerial and ground applicators were made from surrogate studies, using Londax® on rice and WHIP® on soybean, respectively. The greatest potential exposure is likely for pilots, mixer-loaders and flaggers. Ground applicators are anticipated to have much lower exposure than aerial applicators. The season of application of WHIP® is 35 days and it is anticipated that the maximum number of workdays during this period will be 15 days (aerial) or 10 days (ground).

## **Dietary exposure**

The registrant's database suggests that residues will not be present in rice at harvest. Calculations of acute (daily) and chronic (annual) dietary exposure to fenoxaprop-ethyl, using default residue values or tolerances, have been conducted by DPR. The magnitude of the dietary intake of potential residues has been calculated for rice, for other crops for which there are current U.S. EPA tolerances, and from secondary residues in livestock eating treated commodities. The dietary exposure for various population subgroups has been estimated. Non-nursing infants, less than one year old, had the highest potential acute dietary exposure to fenoxaprop-ethyl, whether rice or all commodities with U.S. EPA tolerances, was considered. Children, one to six years old, had the highest potential chronic (annual) exposure, whether rice or all commodities was considered.

## Conclusions

A margin of safety (MOS) of at least 100 is generally recognized as protective of public health when the NOEL is based on toxicology data from animal studies. MOS values were calculated using currently available acute exposure and toxicity data. Mean, short-term worker-exposure data and developmental abnormalities in the rat fetus and mortality in the pregnant monkey, resulted in MOS values above 100 for all categories of worker. When an estimated 95<sup>th</sup> percentile of acute exposure was considered, the MOS values were below 100 for two categories of worker: pilots (71) and flaggers (83). For seasonal aerial exposure, mixer-loaders and flaggers had MOS values, based on liver toxicity in a sub-chronic study, which were above 100. Conversely, a MOS below 100 was estimated for pilots (86). The ground application of WHIP,<sup>®</sup> resulted in a MOS above 100. For reasons discussed, it is likely that the acute and subchronic NOEL values are underestimated and the occupational exposure overestimated; thus, margins of safety calculated in this document are probably lower than under actual use conditions of fenoxaprop-ethyl on rice.

Based on the available toxicity and residue data, DPR concluded that the MOS values for potential acute (daily) and chronic (annual) dietary exposure, for rice and other commodities for which tolerances have been established by U.S. EPA, were above 100 for all population subgroups.

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## I SUMMARY

Fenoxaprop-ethyl is a herbicide which is selective against perennial and annual grass weeds in many crops. It is a member of the aryloxy phenoxy-propionate class of herbicides, and its mechanism of action is to interfere with fatty acid biosynthesis, specifically to inhibit acetyl CoA carboxylase. This enzyme is found both in plant chloroplasts and mammalian liver.

The formulation Whip<sup>®</sup> 1EC, is a 12.5% emulsifiable concentrate of fenoxaprop-ethyl. Registration is currently being requested for this product in California for use as a postemergence rice herbicide. Whip<sup>®</sup> has been registered for use in other states since 1987 by the United States Environmental Protection Agency (U.S. EPA, 1988).

The parent, fenoxaprop-ethyl, is inactive but it rapidly breaks down in the environment to the free acid, fenoxaprop, which is biologically active. This undergoes further degradation to other species containing the 6-chlorobenzoxazol-2-one moiety, which are all considered in the establishment of the tolerances. Residues in rice were below the Limit of Quantification or LOQ (0.05 ppm), which is also the tolerance, within 30 days of application. In 34 field trials on rice, the residues were consistently below 0.02 ppm (Limit of Detection, LOD) after 80 days (Pre-Harvest Interval or PHI).

Environmental chemistry studies conducted with fenoxaprop-ethyl indicate that it should degrade rapidly in the environment and show little, if any, tendency to leach into groundwater.

A human health risk assessment has been conducted for fenoxaprop-ethyl because of low NOEL values for effects reported in animal studies. The risk assessment specifically addresses the potential exposure of workers performing the mixing and application of fenoxaprop-ethyl to rice. The toxicology endpoints used in the assessment were fetal anomalies (rat) and maternal mortality (teratology study using Cynomolgus monkeys) for acute occupational and dietary exposure; systemic toxicity (reduced body weight gain and effects on organ weights, especially liver) for chronic dietary exposure; liver toxicity (increased liver weight and abnormal liver histopathology in a sub-chronic mouse study) for seasonal occupational exposure.

Several (9) developmental toxicity studies have been conducted using fenoxaprop-ethyl involving 4 species: rat, rabbit, mouse and monkey. In only one (rat) study did the NOEL for developmental toxicity (10 mg/kg/day) fall below that for maternal toxicity (32 mg/kg/day). However, in another study, with the Cynomolgus monkey, the developmental NOEL ( $\geq 50$  mg/kg/day) was greater than the maternal NOEL (10 mg/kg/day) and in the other 7 studies, these NOEL values were equivalent. The endpoints for developmental toxicity were increased fetal anomalies (skeletal and visceral); for maternal toxicity, mortality. The NOEL for both maternal and developmental toxicity was, therefore, 10 mg/kg/day.

Subchronic toxicity was measured in four dietary, one dermal and one inhalation studies, using either rat, mouse or dog. The duration of each study was 21-days to 3-months. Signs of possible liver and/or kidney toxicity were consistently observed, the lowest NOEL being 1.9 mg/kg/day for liver toxicity in a 30-day mouse study. In this report, liver toxicity included increased absolute and relative liver weight with abnormal histopathology. Reversibility of hepatic effects, which was noted (in four of these studies) whenever dosing was discontinued for 4 weeks, was not reported in this 30-day mouse study.

Chronic toxicity from repeated exposure to fenoxaprop-ethyl was identified in a 2-year dog study. A fall in body weight gain without a change in food consumption was reported, with a NOEL of 0.9 mg/kg/day. In addition, the liver weight was increased at all dose levels, including the lowest of 0.18 mg/kg/day, at which 16% and 22% increases were reported in absolute and relative weights, respectively. There was not a significant reduction in body weight or body weight gain at this dosage. Because an increase in liver weight alone is not considered to be an adverse effect, a NOEL 0.9 mg/kg/day was considered appropriate for this study.

There was no evidence of oncogenicity in studies conducted with the rat, mouse or dog.

Fenoxaprop-ethyl was not genotoxic in any of the standard battery of *in vitro* and *in vivo* tests.

Reproductive toxicity was measured in two multi-generation studies in rats. In both studies, a NOEL for developmental and maternal effects was established at a dietary concentration of 30 ppm, equivalent to 1.7 mg/kg/day, based on increased liver and kidney weights, nephrocalcinosis and decreased thymus weight at 180 ppm.

The NOEL of 10 mg/kg/day, from the rat and Cynomolgus monkey developmental toxicity studies, was used to determine margins of safety for potential acute occupational and daily dietary exposure. The value of 1.9 mg/kg/day was used to calculate the margins of safety from seasonal occupational exposure. A chronic NOEL value of 0.9 mg/kg/day was used to characterize the margins of safety to consumers from eating treated rice products on an annual basis.

Occupational exposure was estimated using surrogate data: for ground applicators, using a WHIP® study on soybeans; for aerial applicators, using a study conducted using another rice herbicide, Londax.® The Absorbed Daily Dosages (ADD), for ground applicators, ranged from 1.0 to 22 µg/kg/day. For aerial applicators, the mean ADD values were 52 ± 42 µg/kg/day (pilot), 2.9 ± 1.6 µg/kg/day (mixer-loader) and 43 ± 40 µg/kg/day (flagger). The Seasonal Average Daily Dosage (SADD), for ground applicators, ranged from 0.29 to 6.3 µg/kg/day. For aerial applicators, the mean SADD values were 22 µg/kg/day (pilot), 1.2 µg/kg/day (mixer-loader) and 18 µg/kg/day (flagger).

Dietary exposure was estimated using TAS™ software for acute (daily) and chronic (annual) scenarios. Based on the submitted rice residue data, and assuming consumption for the highest percentage of user-days, the 95<sup>th</sup> percentile of potential acute exposure for all 17 population subgroups ranged from 0.029 to 0.233 µg/kg/day. For chronic (annual), dietary exposure, assuming consumption of residues on rice at 50% of the LOD (0.01 ppm), the range of mean exposures was 0.001 to 0.012 µg/kg/day.

Because fenoxaprop-ethyl is registered by U.S. EPA for use on crops other than rice, calculations of dietary exposure were also made for these commodities. For the combined consumption of residues in beef, veal and milk (0.01 ppm, the LOD), rice (0.02 ppm, the LOD) and soybean, wheat, cottonseed, peanut, barley, goat, sheep and pork (0.05 ppm, tolerance), the acute exposure ranged from 0.27 to 1.07 µg/kg/day. The range of exposures for chronic consumption, based on the default level of 50% of these residues, was 0.038 to 0.269 µg/kg/day.

For combined occupational and dietary exposure, assuming the highest likely dietary exposure for workers (0.14  $\mu\text{g}/\text{kg}/\text{day}$ ), the estimated level of exposure for aerial applicators would be within 1% of the calculated occupational ADD and SADD values. For ground applicators, with lower estimated occupational exposure, acute and seasonal values would increase to ranges of 1.1 to 22.4 and 0.42 to 6.5  $\mu\text{g}/\text{kg}/\text{day}$ , respectively.

The MOS values for potential acute, occupational exposure ranged from 450 to 10,000 for ground applicators. The mean MOS values for aerial application activities were 190 (pilot), 3,400 (mixer-loader) and 230 (flagger). At the 95<sup>th</sup> percentile of occupational exposure, the MOS values for pilots (71) and flaggers (83) were below 100. The range of MOS values for ground applicators, based on mean estimated seasonal exposures, were from 300 to 6,600. For aerial applicators, based on mean estimated seasonal exposures, the MOS values were 86 (pilot), 1,600 (mixer-loader) and 110 (flagger).

The margin of safety calculations associated with potential acute dietary exposure were as follows: the MOS value for rice with residue levels of 0.02 ppm (LOD) was greatest for pregnant, non-nursing females (13+ yrs.), at 338,000 and least for non-nursing infants (< 1 yr.), at 43,000. For chronic (annual) dietary exposure (at 0.01 ppm), the highest and lowest MOS values were 1,000,000 and 77,000 for pregnant, non-nursing females (13+ yrs.) and non-nursing infants, respectively. It should be emphasized that these MOS values (acute and chronic) are probably underestimates since, in 34 residue trials conducted by the registrants, no rice samples at harvest contained any residues, even at the LOD.

In the unlikely event of the consumption of rice plus all other commodities for which U.S. EPA tolerances have been established containing residues of fenoxaprop-ethyl at the LOD, for commodities for which data are available (rice, beef, veal, milk) or the tolerances, for all other commodities, the MOS values would range from 36,000 to 9,000 for acute exposure. The population subgroups with these extreme values were non-pregnant, non-nursing females (20+ yrs.) plus seniors and children (1-6 yrs.), respectively. For chronic consumption of combined commodities, containing 50% of these residues, the MOS values were 23,700 to 3,400. The population subgroups with these values were nursing infants and children (1-6 yrs.), respectively.

The MOS values for combined occupational and dietary exposure for aerial applicators would be the same as those associated with only occupational exposure. For ground applicators, the MOS values for combined exposure ranged from 450 to 9,000 (acute) and from 300 to 4,400 (seasonal).

For the consumption of rice containing residues at tolerance (0.05 ppm), the range of potential acute exposure was 0.074 to 0.582  $\mu\text{g}/\text{kg}/\text{day}$ , for all population subgroups. The consumption of rice with residues of fenoxaprop-ethyl at tolerance would result in maximum and minimum MOS values of 135,000 and 17,000, for pregnant, non-nursing females (13+ yrs.), and non-nursing infants (< 1 yr.), respectively.

The MOS values for the consumption of residues in other commodities for which tolerances are established with U.S. EPA have been determined. For acute dietary exposure to fenoxaprop-ethyl in crops at tolerance, the MOS values for soybean, peanut, wheat, cotton and meats are even greater than they are for rice. Only milk, with a range of MOS values from 2,200 to 19,000, had a lower MOS than rice, indicating greater consumption.

A margin of safety of at least 100 is generally recommended to be protective of human health when the toxicology endpoints are derived from animal studies. Based on toxicology studies indicating fetal anomalies, maternal mortality and liver toxicity, MOS values have been derived for potential occupational and dietary exposure. The ground application of WHIP® to rice would result in MOS values above 100 for both acute (short-term) and seasonal worker exposure. For aerial application, mean MOS values estimated for pilots, mixer-loaders and flaggers were all above 100. However, based on the 95<sup>th</sup> percentile of occupational exposure for aerial applicators, the values for pilots (71) and flaggers (83) were below 100. For seasonal occupational exposure, based on maximum loads and applications per season, MOS values for mean seasonal exposure were below 100 for pilots (86) but above 100 for mixer-loaders (1,600) and flaggers (110). For reasons discussed, it is likely that the acute and subchronic NOEL values are underestimated and the occupational exposure overestimated; thus, margins of safety calculated in this document are probably lower than under actual use conditions of fenoxaprop-ethyl on rice.

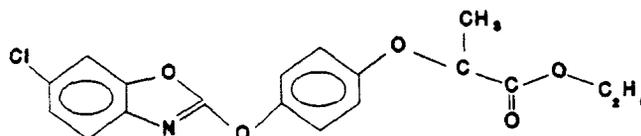
The dietary consumption of rice containing residues of fenoxaprop-ethyl, at the LOD or tolerance, would result in MOS values above 100 for all population subgroups, both for acute and chronic (annual) exposure patterns. Likewise, the consumption of rice plus combined commodities containing residues at estimated worst-case levels (LOD or tolerance) would result in MOS values above 100, for all population subgroups. Dietary exposure to residues in rice would not significantly reduce the MOS values associated with aerial occupational exposure, for combined exposure scenarios.

U.S. EPA tolerances for fenoxaprop-ethyl on rice and on all other commodities for which tolerances have been established, whether consumed alone or in combination, provided acute margins of safety for all population subgroups above 100.

## F. PHYSICAL AND CHEMICAL PROPERTIES (Worthing, 1983)

<b>Chemical Family:</b>	aryloxy-phenoxy-propionate derivatives
<b>Chemical Name:</b>	(±)-ethyl 2-[4-[(6-chloro-2-benzoxazolyl)oxy]-phenoxy]propanoate
<b>Common Name:</b>	Fenoxaprop-ethyl
<b>Trade Names:</b>	Whip <sup>®</sup> , Whip 360 <sup>®</sup> Acclaim <sup>®</sup> , Depon <sup>®</sup> , Excel <sup>®</sup> , Furore <sup>®</sup> , Option <sup>®</sup> , Option II <sup>®</sup> , Bugle <sup>®</sup> , Cheyenne TP <sup>®</sup> , Horizon <sup>®</sup> , Tiller <sup>®</sup>
<b>CAS Number:</b>	66441-23-4

### Chemical Structure:



<b>Empirical Formula:</b>	C <sub>18</sub> H <sub>16</sub> ClNO <sub>5</sub>
<b>Molecular Weight:</b>	361.8 g/mol.
<b>Melting Point:</b>	80-85°C
<b>Boiling Point:</b>	> 300°C at 760 mm Hg
<b>Stability:</b>	Half-life - aqueous media (pH 9) at 20°C, 2.4 days. - aerobic, soil 15 - 21 days (n=3). - anaerobic, soil 28 days. - photolysis, aqueous (pH 5), 54 days. - photolysis, soil, lamp ~ 149 h (≡ 45 days, sun).
<b>Solubility at 25°C:</b>	water: 0.8 - 0.9 mg/kg toluene: > 300 g/kg acetone: > 500 g/kg ethyl acetate: > 200 g/kg cyclohexane, ethanol, octanol: 10 g/kg.
<b>Physical Characteristics:</b>	Colorless solid
<b>Vapor pressure:</b>	3.2 x 10 <sup>-8</sup> mm Hg at 25°C.
<b>K<sub>ow</sub></b>	19,200 (log K <sub>ow</sub> = 4.28).
<b>Density:</b>	≈ 1.3 g/cm <sup>3</sup> at 20°C
<b>pH:</b>	5.4 ± 1 (1% suspension, distilled water)

## G. ENVIRONMENTAL FATE

### Hydrolysis

Fenoxaprop-ethyl has been shown to be stable in weak acid (pH=5), moderately stable in neutral conditions (pH=7) and unstable in weak base, with a half-life ( $t_{1/2}$ ) of 2.4 days at pH9 (Papathakis, 1993).

### Aqueous Photolysis

One preliminary and 3 final reports have been submitted under AB-2021 to the Department of Pesticide Regulation (DPR) describing aqueous photolysis studies. The final reports have all been rejected by DPR, but the data reported in the preliminary report suggest that fenoxaprop-ethyl, exposed to sunlight in a system buffered at pH 5, would have a  $t_{1/2}$  of approximately 54 days (Papathakis, 1993). An acceptable final version of the preliminary report is pending.

### Soil Photolysis

Relative to other routes of soil dissipation, soil photolysis does not appear to be an important contributor to the environmental degradation of fenoxaprop-ethyl. In artificial sunlight, in the only acceptable study, the  $t_{1/2}$  was *circa* 149h, corresponding to 45 days in natural sunlight (Papathakis, 1993).

### Aerobic Soil Metabolism

Under aerobic soil conditions, fenoxaprop-ethyl has been found to degrade rapidly to the free acid, fenoxaprop. Because the free acid has herbicidal activity, its level has been combined with the amount of parent ester in calculating degradation rates (Papathakis, 1993). Using this approach,  $t_{1/2}$  values ranging from 15 to 21 days (n=3) have been obtained.

### Anaerobic Soil Metabolism

Using the same calculation as for aerobic studies, the  $t_{1/2}$  for anaerobic soil metabolism has been determined to be 28 days (Papathakis, 1993).

### Mobility

#### **Soil Adsorption/Desorption**

Five soil adsorption coefficient studies were submitted to DPR and all were considered unacceptable (Papathakis, 1993). However, repeat studies with parent compound are not required by DPR because of the rapid hydrolysis to the free acid. Although the studies did not enable an accurate adsorption coefficient to be determined, they did show that fenoxaprop-ethyl and its soil degradates bind tightly to soil, suggesting that the herbicide is not anticipated to leach. Because of the relative stability of the free acid, fenoxaprop, an acceptable adsorption\desorption study is required for the free acid instead of parent for conditional registration.

## **Leaching Potential**

Two studies used the soil thin layer chromatography method to measure the mobility of <sup>14</sup>C-fenoxaprop-ethyl compared with the mobility of two other herbicides, pyrazon and 2,4-D. The first study showed, using 3 different soils, that fenoxaprop-ethyl is immobile, while pyrazon has low mobility and 2,4-D is mobile (Papathakis, 1993). In the second study, <sup>14</sup>C-fenoxaprop-ethyl was aged in soil for 16 days and the <sup>14</sup>C degradates were then extracted. The relative mobility of the mixture was compared with pyrazon and buturon, again using 3 soil types. It was determined that most fenoxaprop-ethyl degradates were relatively immobile, while a small percentage were moderately mobile. Pyrazon and buturon had low mobility *i.e.* they ranked in between immobile and moderately mobile.

## **Field Dissipation**

Five soil dissipation studies were submitted by Hoechst-Roussel in support of registrations for use on rice (Papathakis, 1993). They were conducted in Mississippi, California, Indiana, Maryland and Louisiana. The Mississippi and California studies, although originally found to be acceptable, have subsequently been rejected due to GLP (Good Laboratory Practice) violations. The application rates were 0.1 to 0.4 lb/A (maximum label rate, 0.3 lb/A) and the half-life of combined residues (parent, fenoxaprop and 6-chloro-2,3-dihydro-benzoxazol-2-one) was 2 to 14 days. In addition, because residues were not found below 7.5 cm, it was concluded that the herbicide does not leach, under these use conditions. The California field dissipation study will be repeated for conditional registration.

Literature reports also indicate rapid soil metabolism, under laboratory and field conditions, combined with low soil mobility. Smith (1985), found that fenoxaprop-ethyl underwent almost complete hydrolysis to the free acid within 24 hours in soils with >65% field moisture capacity; ester hydrolysis was much less in air-dried soil. Toole & Crosby (1989) also evaluated the environmental persistence of fenoxaprop-ethyl by conducting field and laboratory experiments. Rapid dissipation occurred, with  $t_{1/2}$  values of <4 hours and 6 days, respectively, for field and laboratory conditions. Photolysis  $t_{1/2}$  values in field and sterile, distilled water were 29 and 269 hours, respectively. Another study showing rapid hydrolysis of fenoxaprop-ethyl to the free acid in soil under aerobic conditions found that the acid racemized ( $t_{1/2}$  to 4-7 days) yielding ultimately a residue containing 70%R and 30%S enantiomers (Ottmar & Ulrike, 1988).

## **Plant Metabolism**

Two greenhouse and two field studies have been conducted with <sup>14</sup>C-fenoxaprop-ethyl to determine the nature of the residues in rice. In the former studies, rice plants were treated at the 4-5 leaf stage, plant parts being harvested either at or 3-4 weeks before maturity (Papathakis, 1993). The rates of application were 0.083 to 0.17 kg/ha. The residues at harvest were near or below the limit of detection (LOD = 0.02 ppm) in all rice plant parts, which precluded metabolite identification, whereas in the second study, 20% of the (bound or extracted) <sup>14</sup>C contained the 6-chlorobenzoxazol-2-one moiety. All metabolites containing this moiety are included in the submitted plant residue method. The other 80% of the <sup>14</sup>C was characterized as consisting of highly polar species which could not be readily identified.

In the field studies, conducted in Spain, rice plants were treated at the 5-6 leaf stage, flooded at 6 days and leaf samples taken at 22 days; plants were then harvested at maturity. The application rates were 0.07 to 0.1 kg/ha. Several findings were made, first that rice grain contained only traces of <sup>14</sup>C; second, that parent and metabolites translocated very little; third, that 34% of the <sup>14</sup>C recovered in leaf samples at 22 days contained the 6-chlorobenzoxazol moiety (Papathakis, 1993).

### **Plant Residues**

In 5 U.S. residue trials (Papathakis, 1993), rice plant parts were sampled at maturity and analyzed for residues of fenoxaprop-ethyl. At application rates from 0.3 to 0.4 lb/A and pre-harvest interval (PHI) of  $\leq 90$  days, combined residues were  $< 0.05$  ppm (limit of quantification, LOQ) and in some studies, there were no residues above 0.02 ppm (LOD). Processed rice commodities, including grain, straw, bulbs, bran and milled grain contained  $< 0.02$  ppm. A tolerance of 0.05 ppm for residues of fenoxaprop-ethyl and its metabolites in rice has been established by U.S. EPA (40 CFR 180.430).

### III TOXICOLOGY PROFILE

#### A. PHARMACOKINETICS

##### Oral Biotransformation-Rat

Biotransformation of  $^{14}\text{C}$ -fenoxaprop-ethyl in the rat has been reported in 3 separate studies (Dorn *et al.*, 1982, 1985; Burkle *et al.*, 1985). These have used  $^{14}\text{C}$ -fenoxaprop-ethyl labelled in either the chlorophenyl or dioxyphenyl ring system (Specific activity 2.635 to 22.85 mCi/g; radiochemical purity 96 to 98%). Single oral dosing of Wistar rats of both sexes at 2, 10 and 40 mg/kg led to the identification of the following metabolites: fenoxaprop (free acid), in both urine ( $\leq 27\%$ ) and feces; 2-(4-hydroxyphenoxy)-propionic acid (HPP-acid) in the urine (48% at 2 mg/kg, both sexes); a mercapturic acid of 6-chlorobenzoxazol formed by conjugation of this metabolite to glutathione followed by cleavage of glycine and glutamate, comprising 50% of urine radioactivity, and also a bound form in the feces. Three other identified urinary metabolites contributed  $< 5\%$  each.

##### Oral Absorption and Elimination-Rat

The absorption and elimination of  $^{14}\text{C}$ -fenoxaprop-ethyl has also been studied in the rat in 3 separate studies: oral and intravenous administration (Kellner & Eckert, 1982); single oral administration (Kellner & Eckert, 1984a); repeat oral administration (Kellner & Eckert, 1984b). All of these studies used chlorophenyl U- $^{14}\text{C}$ -HOE 33171 of specific activity 12.02 to 26.34 mCi/g and radiochemical purity  $\geq 98\%$ .

In the first study, a single dose of 2.06 to 2.52 mg/kg of  $^{14}\text{C}$  parent was administered to groups of 5 SPF Wistar rats/sex/route (Kellner & Eckert, 1982). Using the oral method, the maximum blood concentrations of radiolabel were 3.73 (M) and 4.53 (F)  $\mu\text{g/ml}$ , peaking at 6 to 8h after dosing. The elimination was biphasic with  $t_{1/2}$  values of 14.6h (M), 6.4h (F) for the rapid phase and 74.2h (M & F) for the slower phase. Intravenous administration resulted in similar blood levels, indicating that absorption following oral dosing was almost complete. Maximum blood levels of  $^{14}\text{C}$ , occurring at 5 min., were 4.22 (M) and 5.12 (F)  $\mu\text{g/ml}$ . Elimination was tri-phasic with  $t_{1/2}$  values of 1.3, 11.2, and 97.5h (M) and 0.72, 7.8 and 72.8h (F). The amount of radiolabel eliminated as  $^{14}\text{CO}_2$  was below the detection limit of 0.01% of applied  $^{14}\text{C}$  ( $\sim 0.2$  ppb).

In the second study, a single oral dose of 10 mg/kg of  $^{14}\text{C}$ -fenoxaprop-ethyl was administered to 5 SPF Wistar rats/sex and the absorption and elimination was determined for 7d (Kellner & Eckert, 1984a). The radiolabel was excreted via both urine, 44% (M) and 60% (F), and feces 49% (M) and 35% (F). The elimination was biphasic, with a rapid, initial Phase I having  $t_{1/2}$  values from 8 to 10h into urine and feces, for both sexes. Phase II  $t_{1/2}$  values were, for urine, 36h (M) and 69 h (F) and, for feces, 45h (M) and 27h (F). The highest concentrations of  $^{14}\text{C}$  were found in fatty tissues and kidney.

In a repeat oral study, 2 mg/kg/day of fenoxaprop-ethyl was administered for 14 successive days to SPF Wistar rats, 5 per sex, followed by 2 mg/kg of  $^{14}\text{C}$  material (Kellner & Eckert, 1984b). Radiolabel moved into urine and feces with  $t_{1/2}$  values from 8.5 to 12.5h for urine and feces (both sexes) and the elimination of  $^{14}\text{C}$  was biphasic, with  $t_{1/2}$  values of 72.5h (M), 41.3h (F) from urine and 27.3h (M) and 33.7h (F) from feces. The highest residues were found in kidney, fatty tissue and blood, but there was no tendency for parent or metabolites to accumulate. Indeed, over 50% of radiolabel was excreted within 24 hours, over 75% in 48 hours and 94% within 86 to 168 hours.

### Oral-Comparative Biotransformation

The comparative metabolism of  $^{14}\text{C}$ -fenoxaprop-ethyl was studied by oral administration to pregnant rabbits, rats and a Cynomolgus monkey for the purpose of determining whether there were differences between rodents and primates in fenoxaprop-ethyl pharmacokinetics (Dorn *et al.*, 1984). Unlabelled material was administered daily to (5) rats and (5) rabbits at 50 mg/kg/day and to the monkey at 10 mg/kg/day during the period of embryo organogenesis; days 7 to 16 (rats), days 7 to 19 (rabbits) and days 20-50 (monkey). The first and last doses for the monkey and the final dose for the others was labelled with  $^{14}\text{C}$ . After correcting for dose, the blood level in the monkey was the lowest. Within each species, the highest  $^{14}\text{C}$  levels were found in the kidney, liver and blood. The  $^{14}\text{C}$  content was higher in rat than rabbit fetuses at 6h (ratio, 10 to 1.5). Higher levels of the free acid were found in rat than in rabbit livers, suggesting greater hydrolytic capability in the rat. A mercapturic acid of 6-chlorobenzoxazol was found in all 3 species, but at a lower level (1/3) in the monkey than the other species, perhaps reflecting the lower levels of glutathione transferase in primates than in rats or rabbits (Chasseaudd, 1973; Hayakawa *et al.*, 1974). The qualitative similarity of the metabolite profile in all test species suggests a similar pattern in humans.

## **B. ACUTE TOXICITY**

### **Technical and 12.5 EC Formulation**

Several acute toxicity studies have been completed using technical fenoxaprop-ethyl and the 12.5 EC formulation. The results are summarized in **Tables 1 and 2**.

### Clinical Observations (acute)

The following effects were reported in acute oral  $\text{LD}_{50}$  toxicity studies in rats and mice: passiveness, disequilibrium, squatting, crawling, bristled hair, blepharophimosis, rhinorrhea, chromodacryorrhea, increased lacrimation, jerky or increased respiration and drowsiness.

### Necropsy findings (acute)

Mortality occurred within 7 days of dosing. Dead rodents revealed the following abnormalities: spots and markings on the liver/hepatic lobules, diffused reddening of pancreas, petechial hemorrhages in the gastric mucosa (fundic part) and red-black matter in the entire small intestine.

**Table 1 Acute toxicity of technical fenoxaprop-ethyl.**

Route/Species	Sex	Results	Reference <sup>a</sup>
<u>Oral LD<sub>50</sub></u> (C.I.) <sup>b</sup>			
Rat	M	2357 (2240-2479) mg/kg <sup>c</sup>	1
Rat	F	2500 (2230-2780) mg/kg <sup>c</sup>	2
Mouse	M	4670 (4180-5130) mg/kg <sup>c</sup>	3
Mouse	F	5490 (5010-6140) mg/kg <sup>c</sup>	4
<u>Dermal LD<sub>50</sub></u>			5
Rat	F	> 2000 mg/kg <sup>c</sup>	
<u>Inhalation LC<sub>50</sub></u>			6
Rat	M/ F	> 0.511 mg/l; > 92 mg/kg <sup>d</sup>	
<u>Eye Irritation</u>			7
Rabbit		Category II	
<u>Dermal Irritation</u>			7
Rabbit		Category III	
<u>Dermal Sensitization</u>			8
Guinea pig		Category IV	

a/ (1) Hollander & Weigand, 1979a. (2) Hollander & Weigand, 1979b. (3) Mayer & Weigand, 1979a. (4) Mayer & Weigand, 1979b. (5) Hollander & Weigand, 1979c. (6) Hollander & Leist, 1982. (7) Hollander & Weigand, 1979d. (8) Jung & Weigand, 1982.

b/ 95% Confidence interval

c/ Unacceptable and not upgradeable because single sexes were used for separate studies; collectively, they satisfy FIFRA (Federal Insecticide, Fungicide and Rodenticide Act) requirements.

d/ based on measured concentrations, 4h exposure, and a default inhalation rate of 0.175 l/min.(U.S. EPA, 1990).

**Table 2 Acute toxicity of fenoxaprop-ethyl: the 12.5 EC formulation.**

Route/Species	Sex	Results	Reference <sup>a</sup>
<u>Oral LD<sub>50</sub></u> (C.I.)			
Rat	M	3310 (2770-3740) mg/kg <sup>b</sup>	1
Rat	F	3400 (3050-3860) mg/kg <sup>b</sup>	2
<u>Dermal LD<sub>50</sub></u>			
Rat	M	> 2000 mg/kg <sup>b</sup>	3
Rat	F	> 2000 mg/kg <sup>b</sup>	4
<u>Inhalation LC<sub>50</sub></u>			
Rat	M/F	3.92 (3.24-4.28) mg/l; 710 (590-780) mg/kg <sup>c</sup>	5
<u>Eye Irritation</u>			
Rabbit		Category II	6
<u>Dermal Irritation</u>			
Rabbit		Category III	6

a/ (1) Mayer & Weigand, 1982a. (2) Mayer & Weigand, 1982b. (3) Mayer & Weigand, cd.

(4) Mayer & Weigand, de. (5) Hollander & Weigand, 1982. (6) Leist & Weigand, 1982.

b/ Unacceptable and not upgradeable because single sexes were used for separate studies; collectively, they satisfy FIFRA requirements.

c/ Based on measured concentrations, 4h exposure, and a default inhalation rate of 0.175 l/min. for 250 g rat (U.S. EPA, 1987).

### C. SUBCHRONIC TOXICITY.

#### Dietary-Rat

In an acceptable, definitive study, 30 Wistar SPF71 rats/sex/dose were fed diets containing 0, 20, 80 or 320 ppm fenoxaprop-ethyl (HOE 33171; 96% pure) for 3 months; ten rats from each group were kept for a 4-week recovery period (Donaubauer *et al.*, 1981). These were equivalent to dosages of approximately 1.6, 6.3 or 25.3 (male) and 1.7, 6.9 or 27.5 (female) mg/kg/day. The only significant compound-related effects were reported in males dosed at 25.3 mg/kg/day: increased absolute liver weight (115% of control,  $p < 0.05$ ); increased serum alkaline phosphatase activity (119% of control,  $p < 0.05$ ) and enlarged centrilobular hepatocytes with fine eosinophilic granulation of the cytoplasm. All of these effects were reversible after a recovery period of 4 weeks. The NOEL was 80 ppm, male, or 6.3 mg/kg/day, and 320 ppm, female, equivalent to 27.5 mg/kg/day (Table 3).

#### Dietary-Mouse

A supplementary study was conducted with SPF71 mice (10 mice/sex /dose) subjected to a diet containing fenoxaprop-ethyl (HOE 33171, purity not stated) at 0, 5, 10, 20 or 80 ppm, equivalent to 0, 0.9, 1.8, 3.5 or 14.4 (male) and 0, 1.0, 1.9, 3.5 or 15.4 (female) mg/kg/day for 30 days (Leist *et al.*, 1981). There were no compound-related changes in behavior, general health, body weight or food consumption. There was an increase in the blood cholesterol level at 80 ppm, in females, and an increase in total lipids at 20 and 80 ppm,

in males. There were increases in absolute and relative liver weight at doses down to 20 ppm for females (115% of control,  $p < 0.05$ ) and 80 ppm for males (125% of controls,  $p < 0.05$ ). Histopathological abnormalities included dose-dependent changes in hepatic epithelia with large nuclei and dense eosinophilic cytoplasm in the centrilobular regions of the liver. Reversibility was not noted in this study. Based on these hepatic effects, the NOEL values were 20 ppm (M), or 3.5 mg/kg/day and 10 ppm (F), equivalent to 1.9 mg/kg/day.

### **Dietary-Dog**

Pure-bred Beagle dogs, 2/sex/dose, were fed a diet containing fenoxaprop-ethyl (HOE 33171, 97% pure) at 0, 80, 400 or 2000 ppm, equivalent to 5.9, 29.4 or 147 (male) and 4.9, 24.3 or 122 (female) mg/kg/day for 30 days in a supplementary study (Brunk *et al.*, 1980). All dogs at 2000 ppm were killed prematurely owing to moribund conditions, associated with fatty degeneration of the liver and elevated alkaline phosphatase activity and atrophy of the splenic capsule and thymus. At 400 ppm, a single male displayed siderosis of the lung, atrophy of the thymus and hyperplasia of the lymph follicles of the thyroid. The NOEL was 80 ppm, equivalent to 5.9 (M) or 4.9 (F) mg/kg/day, based on the organ effects described.

In a subsequent study, which was considered unacceptable according to FIFRA guidelines due to lack of diet analysis, the effects of fenoxaprop-ethyl (HOE 33171, 96% pure) were studied at concentrations of 0, 16, 80 or 400 ppm in the daily diet for 3 months, using 6 beagle dogs/sex/dose (Brunk *et al.*, 1981). These were approximately equivalent to 1.2, 5.9 or 29 (M) and 1.0, 4.9 or 24 (F) mg/kg/day. Of these, 2 dogs/sex/dose were maintained for a further 4 weeks to monitor recovery. All dogs survived the study period with no treatment-related changes in clinical signs, body weight, food consumption, hematology and clinical chemistry. Chronic interstitial pyelonephritis was detected in 3/6 high dose males and females and 3/6 mid-dose males. One of these cases was diagnosed in a mid-dose male after the recovery period. The NOEL was 16 ppm *i.e.* 1.2 (M) or 1.0 (F) mg/kg/day, based on chronic interstitial pyelonephritis.

### **Dermal-Rat**

Fenoxaprop-ethyl (HOE 33171, 96.5% pure) dissolved in sesame oil, was applied to the shaved skin, covered with an occlusive dressing for 6 hours/day, 5 days/week for 21 applications to 6 rats/sex/dose at 20, 100 or 500 mg/kg/day in an acceptable dermal, sub-chronic study (Ullmann *et al.*, 1984a). An additional 5 rats/sex for the control, mid and high dose animals were monitored for a further 4 weeks to observe recovery. All rats survived until the end of the study. Reduced body weight at the highest dose (91% of control,  $p < 0.05$ ) and reduced food consumption were observed. A dose-related increase in relative liver weight (116-140% of control,  $p < 0.01$ ) without any abnormal histopathology was recorded in high and mid-dose rats. High-dose animals also displayed increased absolute and relative kidney weights (117% of control,  $p < 0.05$ ). The NOEL was 20 mg/kg/day, based on changes in relative liver and kidney weights.

In two other 21-day rat dermal studies, the dosages of 5 to 20 mg/kg/day were too low to produce symptoms other than slight scales and erythema at the HDT, which were reversible (Ullmann *et al.*, 1987a,b). These reports were considered unacceptable and supplementary, respectively.

### **Inhalation-Rat**

Groups of 6 rats/sex/dose were exposed (nose only) to particles of HOE 33171 (96.5% pure) at measured concentrations of 0, 0.014, 0.073, 0.248 or 0.727 mg/l for 6 h/day, 5 days/week for 28 exposures in an acceptable inhalation toxicity study (Leist *et al.*, 1984c). An additional 5 rats/sex/dose underwent the same

treatment regime in order to monitor recovery. There were dose-related increases in absolute and relative liver and kidney weights ( $p < 0.05$ ) at doses of 0.073 mg/l and above. At 0.248 and 0.727 mg/l, centrilobular hepatocellular hypertrophy was reported (M and F) along with elevated serum alkaline phosphatase. The latter effect was observed at 0.073 and 0.248 mg/l (M) and, at the high dose, for both sexes. After a 4-week recovery period, no treatment-related effects for these two parameters of toxicity were detectable. The NOEL was determined to be 0.014 mg/l (M and F), equivalent to 3.54 mg/kg/day, based on the liver and kidney weight changes described.

**Table 3 Summary of subchronic toxicity studies of technical fenoxaprop-ethyl.**

**a. ORAL-DIETARY**

Study/Species	Sex	Dosage (mg/kg/day)	Effect	LOEL (mg/kg/day)	NOEL (mg/kg/day)	Ref. <sup>a</sup>
3-month/rat	M	1.6-25.3	liver toxicity <sup>b,f</sup>	25.3	6.3	1
	F	1.7-27.5		n.d. <sup>c</sup>	27.5	
30-day/mouse	M	0.9-14.4	liver toxicity <sup>b</sup>	14.4	3.5	2
	F	1.0-15.4		3.5	1.9	
30-day/dog	M	~5.9-147	liver toxicity	29.4	~5.9	3
	F	~4.9-122		24.3	~4.9	
3-month/dog	M	1.2-24.3	kidney toxicity <sup>d,f</sup>	5.9	1.2	4 <sup>e</sup>
	F	1.0-29.4		4.9	1.0	

**b. DERMAL**

21-day/rat	M	20-500	liver and kidney toxicity <sup>b,f</sup>	100	20	5
	F	20-500		100	20	

**c. INHALATION**

Study/Species	Sex	Dose <sup>g</sup>	Effect	LOEL (mg/l) (mg/kg/d)	NOEL (mg/l) (mg/kg/d)	Ref. <sup>a</sup>
6-week/rat	M/F	0.014-0.727 mg/l	liver, kidney toxicity <sup>b,f</sup>	0.073	0.014	6
		3.54-184 mg/kg/d		18.4	3.54	

a/ (1) Donaubauer *et al.*, 1981. (2) Leist *et al.*, 1981. (3) Brunk *et al.*, 1980. (4) Brunk *et al.*, 1981. (5) Ullmann, 1984a. (6) Leist *et al.*, 1984c.

b/ increased weight and abnormal histopathology.

c/ not determined.

d/ interstitial pyelonephritis

e/ unacceptable, no analysis of test diet.

f/ reversible

g/ default inhalation rate of 0.175 l/min. (250 g rat) used to convert concentration to dosage (U.S. EPA, 1987).

## D. CHRONIC TOXICITY and ONCOGENICITY

### Dietary-Rat

Technical grade fenoxaprop-ethyl (HOE 33171; 94.9% pure) was administered in the diet to Wistar rats at 0, 5, 30 or 180 ppm for 24 months in a study which was acceptable according to FIFRA guidelines (Kramer *et al.*, 1984). The equivalent dosages were 0.3, 1.6 or 9.4 (M) and 0.3, 2.0 or 11.9 mg/kg/day (F). There were 36 rats per sex per group of which 6 of each sex were used for hepatic and renal function tests and 10 of each sex for monitoring residues in organs and tissues. Additional supplementary studies included two interim sacrifices of a further 10 rats/sex/dose, at 6 months (Kramer *et al.*, 1983a) and 12 months (Kramer *et al.*, 1983b). The equivalent dosages were 0.3, 2.0 or 11.9 (M) and 0.4, 2.5 or 14.6 (F) mg/kg/day, at 6 months, and 0.3, 1.7 or 10.2 (M) and 0.4, 2.1 or 13.3 (F) mg/kg/day, at 12 months.

In the two interim studies, all animals survived until scheduled termination except for one low-dose male which died during week 3 due to bladder hemorrhage in the 6-month study. In the 2-year study, mortality of treated animals was very similar to controls. There were no treatment-related changes in food consumption or body weight, except for an increased body weight (110% of control,  $p < 0.05$ ) without an increase in food consumption for high dose males in the 6-month study. In this interim report, an increase in absolute and relative kidney weight was also noted in females at 180 ppm. An increase was observed in hyperplastic epithelia of the renal pelvis with calcareous deposits, these being more common than in control at 6, 12 and 24 months. The increased number of calcareous deposits at 24 months was significantly above the control level for males and combined sexes at 30 ppm and 180 ppm ( $p < 0.02$  and  $p < 0.005$ , respectively). However, there was an apparent reduction in the level of calcareous deposits in control males with increasing age. This makes the effect at 30 ppm of doubtful toxicological relevance. At 12 months, high dose animals showed elevated activity of two enzymes: aminopyrine N-demethylase (224% of control,  $p < 0.05$ ) in females and carnitine acetyltransferase (403-538% of control,  $p < 0.05$ ) in both sexes. These were among eleven enzymes monitored to assess hepatotoxicity. Histological examination revealed distension of the zona reticularis and medulla of the adrenals in high dose rats at both 12 and 24 month intervals, in both sexes. The adrenal weight (absolute and relative) was significantly higher in males at 30 and 180 ppm at 12 months. At 24 months, the only other effects observed were a reduction in absolute and relative liver weights (89% and 90%, respectively,  $p < 0.05$ ) in high-dose males compared with control (Table 4). The investigators did not consider the effects on liver or kidney weights to be of toxicological relevance in the absence of abnormal histological changes or functional disturbances. The residue levels in the organs and tissues were dose-related but there were no sex differences and no time-related accumulation. The NOEL at 24 months was considered to be 30 ppm (1.6, M or 2.0, F mg/kg/day) based on the increased incidence of calcareous deposits in the renal pelvis, effects on liver weight and the effects on adrenal histology, at 180 ppm.

In an acceptable satellite study, rats (60 rats/sex/dose) were exposed to fenoxaprop-ethyl (HOE 33171; 94.0% pure) in the diet at identical concentrations for 28 months (Kramer *et al.*, 1985a). These were equivalent to dosages of 0, 0.3, 1.5 or 9.1 mg/kg/day for males and 0, 0.3, 2.0 or 11.7 mg/kg/day for females. No treatment-related effects were observed in mortality, body weight, food consumption, hematological parameters or urinalysis. In high dose males, a lowering of serum cholesterol (78% of control,  $p < 0.05$ ) and total lipids (76% of control,  $p < 0.05$ ) was recorded. There was an absence of abnormal histology or hepatic function at 28 months (Table 4). No oncogenic potential was noted at 24 or 28 months (Kramer *et al.*, 1984; Kramer *et al.*, 1985a). The NOEL value, based on similar effects to those observed at 24 months, was 30 ppm, equivalent to 1.5 (M) or 2.0 (F) mg/kg/day.

**Table 4** Absolute and relative mean liver weights of rats exposed to fenoxaprop-ethyl in the diet for 12 months (Kramer *et al.*, 1983b), 24 months (Kramer *et al.*, 1984) and 28 months (Kramer *et al.*, 1985a).

Parameter	Sex	Dose (ppm) <sup>c</sup>			
		0	5	30	180
12 MONTHS					
Liver wt. absolute <sup>a</sup>	M	14.2±2.0 (10)	14.2±1.5 (10)	13.4±2.5 (10)	14.5±1.3 (10)
	F	8.8±1.1 (10)	8.5±.8 (10)	8.2±1.0 (10)	8.0±1.5 (10)
Liver wt. relative <sup>b</sup>	M	2.9±.3 (10)	2.7±.2 (10)	2.6±.3 (10)	2.7±.1 (10)
	F	3.1±.4 (10)	2.9±.2 (10)	2.8±.3 (10)	2.9±.5 (10)
24 MONTHS					
Liver wt. absolute <sup>a</sup>	M	16.8±2.7 (25)	16.5±1.8 (19)	15.5±1.7 (23)	14.9±1.5* (21)
	F	11.3±2.6 (18)	11.8±3.6 (17)	10.0±1.5 (16)	10.3±1.4 (19)
Liver wt. relative <sup>b</sup>	M	3.2±.3 (25)	3.0±.2 (19)	3.0±.3 (23)	2.8±.3* (21)
	F	3.3±.4 (18)	3.3±.5 (17)	3.1±.3 (16)	3.2±.3 (19)
28 MONTHS					
Liver wt. absolute <sup>a</sup>	M	16.4±2.2 (41)	15.8±2.5 (39)	15.1±1.9 (43)	15.4±1.9 (44)
	F	11.4±2.1 (39)	10.9±1.7 (40)	10.9±1.8 (35)	10.7±1.8 (33)
Liver wt. relative <sup>b</sup>	M	3.3±.4 (41)	3.2±.4 (39)	2.9±.4* (43)	3.0±.3* (44)
	F	3.4±.4 (39)	3.4±.4 (40)	3.4±.5 (35)	3.2±.3 (33)

a/ absolute weight in g ±S.D..(number of animals).

b/ relative weight in % ±S.D..(number of animals).

c/ equivalent dosages were: 0.3, 1.7 or 10.2 (M) and 0.4, 2.1 or 13.3 (F) mg/kg/day (12 months).

0.3, 1.6 or 9.4 (M) and 0.3, 2.0 or 11.9 (F) mg/kg/day (24 months).

0.3, 1.5 or 9.1 (M) and 0.3, 2.0 or 11.7 (F) mg/kg/day (28 months).

\* significantly different from control at p<0.05 (Sidak test, absolute wt.; Nemenyi/Sidak test, relative wt.).

### Dietary-Mouse

Technical fenoxaprop-ethyl (HOE 33171; 94% pure) was administered to SPF71 mice in the diet at dose levels of 0, 2.5, 10 or 40 ppm to 50 mice/sex/dose for 24 months (Kramer *et al.*, 1985b). An additional study investigated 10 mice/sex/dose, under identical conditions for 12 months (Kramer *et al.*, 1983c). The reports were considered acceptable and supplementary, respectively. These dietary levels were equivalent to 0.35, 1.3 or 5.5 (12 months) and 0.34, 1.4 or 5.5 (24 months) mg/kg/day for males and 0.43, 1.6 or 6.6 (12

months) and 0.40, 1.6 or 6.5 (24 months) mg/kg/day for females. In neither study were there any changes in body weight or food consumption, hematological parameters, clinical signs or abnormal histological findings which were related to treatment. There was a dose-related increase in absolute and relative kidney weight in both sexes in the 12-month study but not in the 24-month one. This difference was statistically significant (108% of control;  $p < 0.05$ , Dunnett's test) only for relative kidney weight in high dose females, partly due to greater variability among males; the kidney effect was not considered toxicologically relevant in the absence of histological abnormalities. Similarly, in the final study, but not the interim one, there was a significant decrease in relative liver weight in mid and high-dose females (85% of control;  $p < 0.05$ , Nemenyi/Sidak test) without any apparent abnormal histology (Table 5). This liver effect alone, was not considered adverse. Therefore, in both studies the NOEL was  $\geq 40$  ppm (5.5 mg/kg/day) for males, at 12 and 24 months. For females, the NOEL at 12 months, based on the increases in absolute and relative kidney weight, was 10 ppm (1.6 mg/kg/day). At 24 months, the NOEL was  $\geq 40$  ppm ( $\geq 6.5$  mg/kg/day) for females, based on no effects at the HDT.

**Table 5 Absolute and relative mean liver weights of mice exposed to fenoxaprop-ethyl in the diet for 24-months (Kramer *et al.*, 1985b).**

Parameter	Sex	Dose (ppm) <sup>c</sup>			
		0	2.5	10	40
Liver wt. absolute <sup>a</sup>	M	1.73 ± .34 (36)	1.72 ± .27 (29)	1.72 ± .24 (29)	1.83 ± .29 (31)
	F	2.01 ± .52 (29)	1.76 ± .41 (20)	1.69 ± .20 (24)	1.71 ± .31 (30)
Liver wt. relative <sup>b</sup>	M	4.77 ± .70 (36)	4.73 ± .66 (29)	4.65 ± .59 (29)	4.93 ± .71 (31)
	F	5.84 ± 1.26(29)	5.19 ± 1.10(20)	4.96 ± .65 (24)*	5.02 ± .71 (30)*

a/ absolute weight in g ± S.D.,(n), at 24 months.

b/ relative weight in % ± S.D.,(n), at 24 months.

c/ equivalent dosages were: 0.34, 1.4 or 5.5 (M) and 0.4, 1.6 or 6.5 (F) mg/kg/day.

\* significantly different from control at  $p < 0.05$  (Nemenyi/Sidak test).

### **Dietary-Dog**

Fenoxaprop-ethyl (HOE 33171; 94% pure) was administered in the diet to beagle dogs, 6 animals/sex/dose at 0, 3, 15 or 75 ppm for 2 years (Brunk & Kramer, 1985). In an interim report, Brunk *et al.*, 1984 presented the results of a similar 1-year study, also using 6 dogs/sex/dose. These doses were equivalent to 0, 0.20, 1.1 or 5.2 mg/kg/day (male) and 0, 0.18, 0.90 or 4.6 mg/kg/day (female) for the 2-year study and approximately 0.20, 1.0 or 5.0 mg/kg/day (male) and 0.16, 0.80 or 4.0 mg/kg/day (female) for the 1-year study. Both studies were acceptable according to FIFRA guidelines.

In the 1-year study (Brunk *et al.*, 1984), except for one mid-dose male which was sacrificed on day 106 due to poor health, all of the dogs survived to study termination without any observed treatment-related changes in body or organ weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, necropsy and histology or hepatic and renal function. Thus, the NOEL was  $\geq 75$  ppm (5

mg/kg/day, male; 4 mg/kg/day, female) with no effects detected at the highest dose tested.

In the 2-year study, a significant decrease in body weight was measured at 15 and 75 ppm ( $p < 0.05$ ) in both sexes (Table 6) without a significant reduction in food consumption (Brunk & Kramer, 1985). There was also a significant reduction in body weight gain at the highest dose for both sexes, 55% of control weight gain for males and 49% for females ( $p < 0.05$ ). The reduction in final body weight at the high and mid-doses is considered to be of less toxicological significance, especially since this parameter was unaffected at 12 months. The liver showed an increase in absolute and relative weight during the course of the study, at all dose levels. However, an effect on liver weight, alone, was not considered an adverse effect without additional evidence of toxicity. There were no other reported effects, on the same parameters as were recorded in the 1-year study. Hepatic and renal function tests were conducted at the start and end of both 1 and 2-year studies and at 3-month intervals during the course of each study. The activities of enzymes which are indicative of specific hepatotoxic events, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and lactate dehydrogenase, were measured in the serum and found to be within the normal range. There were no dose or time-dependent trends in the activity of any of these enzymes which were treatment-related.

Based on the reduction in body weight gain at 75 ppm, combined with increases in absolute and relative liver weight, the NOEL was considered to be 15 ppm. This was equivalent to 1.1 (M) or 0.9 (F) mg/kg/day.

**Table 6 Summary of the chronic effects on mean body weight and mean body weight gain in the dog after exposure to fenoxaprop-ethyl in the diet for 24-months (Brunk & Kramer, 1985).**

Parameter	Sex	Dose (ppm) <sup>a</sup>			
		0	3	15	75
Body weight, final, kg	M <sup>b</sup>	17.1	16.5	15.2*	15.5*
	F <sup>b</sup>	15.9	15.0	15.1*	13.9*
Body weight, gain, kg	M	3.52	2.92	2.65	1.92*
	F	3.73	3.03	3.38	1.83*

a/ equivalent to dosages of 0.20, 1.1 or 5.2 (M) and 0.18, 0.90 or 4.6 (F) mg/kg/day.

b/ 6 animals/dose group.

\* significantly different from control at  $p < 0.05$  (Dunnett's test).

## E. GENOTOXICITY

### Gene Mutation

Bacterial gene mutation experiments were described in two reports (Engelbart, 1979; Hoechst AG, 1982) of which only the latter was acceptable under federal testing guidelines. In the first study, 4 strains of *Salmonella typhimurium* were subjected to one of 5 doses (+ zero control) of test agent at  $\leq 1,500 \mu\text{g}/\text{plate}$ , without rat S9 mixture and  $2,500 \mu\text{g}/\text{plate}$ , for S9 only. This study showed that there was no evidence of mutagenicity but, because there was no cytotoxicity at the HDT, the study was considered unacceptable. A repeat study was conducted with an additional (5<sup>th</sup>) strain of *S. typhimurium*, a strain of *Escherichia coli* and a preliminary cytotoxicity test to justify dose selection (Hoechst AG, 1982). After 48 to 72h incubation at 37°C, positive controls showed mutations in all strains, but there was no test-article induced mutagenic activity. In an acceptable study using the yeast *Schizosaccharomyces pombe*, HOE 33171 (94% pure) was applied at 4 doses (+ zero control), both with and without a rat liver S9 microsomal mixture (Mellano, 1982a). After 4h exposure and 5 days incubation at 32°C, there was no test-article related mutagenic activity.

### Structural Chromosomal Aberrations

Human lymphocytes were exposed to HOE 33171 (94% pure) at 0, 1, 10, 100, 1000  $\mu\text{g}/\text{ml}$ , with and without rat S9 liver microsomes, for 3h at 37°C in an acceptable study (Mellano, 1982b). Chromosome aberrations were measured by recording the abnormal metaphases from 100 metaphases/dose. Cytotoxicity at the HDT was measured as  $> 80\%$  decline in the number of metaphases. There was no test-article dependent increase in the number of chromosome aberrations and thus, no clastogenic activity.

In a second study, which was unacceptable because of an inadequate experimental protocol, NMR1 mice were exposed twice to HOE 33171 (93% pure) by gavage at 0, 18, 180 or 1800 mg/kg (Leist & Jung, 1984). There was no test-article related increase in micronucleus formation or change in (polychromatic to normochromatic) cell ratio. Thus, no clastogenic activity or changes in cell dynamics in bone marrow were observed.

### Unscheduled DNA Synthesis (UDS)

Wistar rat hepatocyte cultures were exposed to HOE 33171 (96.5% pure) at 0, 1, 3.33, 10, 33.33 or 100  $\mu\text{g}/\text{ml}$  for 3h with <sup>3</sup>H-Tdr, in sextuplicate, in a study which was acceptable (Miltenburger, 1987). The assay was completed in the presence of 15 mM hydroxyurea to inhibit S-phase DNA synthesis and UDS was measured using LSC. There was no UDS and it was concluded that fenoxaprop-ethyl did not induce DNA repair in the hepatocytes used.

Two other UDS studies were considered unacceptable because of inadequate positive control data. They showed that fenoxaprop-ethyl probably does not cause mitotic gene conversion in the yeast *Saccharomyces cerevisiae* (Mellano, 1982c) or UDS in cultured HeLa cells (Mellano, 1982d).

In summary, these studies indicate that there is no evidence of genotoxicity under the experimental conditions using fenoxaprop-ethyl. Both with and without metabolites, it had no effect in gene mutation, structural chromosome aberration and UDS experiments.

## F. REPRODUCTIVE TOXICITY

### Dietary-Rat

In a 2-generation rat reproduction study, which was acceptable according to FIFRA guidelines, measurements were made of the effects of HOE 33171 (94% purity) on reproductive performance, using the Sprague Dawley strain of rat, (30/sex/dose) for both F<sub>0</sub> and F<sub>1</sub> (Tesh *et al.*, 1985). The diets, containing 0, 5, 30 or 180 ppm, gave rise to dosages of 0, 0.3, 1.7 or 10.2 (male) and 0, 0.5, 2.7 or 16.4 (female) mg/kg/day for F<sub>0</sub>; 0, 0.4, 2.3 or 13.7 (male) and 0, 0.5, 3.0 or 17.3 (female) mg/kg/day for F<sub>1</sub>. There were two generations and two matings/generation. No treatment-related effects were reported on adult mortality, signs, body weight, food consumption, estrus cycle, pre-coital interval, mating performance, conception rate, gestation length, gestation indices, live births, viability, sex ratios or developmental parameters. At necropsy there were no macroscopic lesions but histopathological examination revealed increased nephrocalcinosis in offspring and adult females. Changes in organ weights in both sexes were detected at 180 ppm, as follows: increased relative liver and kidney weights in both adults and offspring ( $p < 0.001$ , Student's t test); decreased absolute thymus weight in offspring ( $p < 0.001$ ). Effects on liver and kidney weights were observed for each litter of both generations (both sexes). Reduced thymus weight was reported for F<sub>1</sub>A and F<sub>2</sub>B (both sexes). The NOEL was 30 ppm for adult (systemic) and developmental toxicity, equivalent to 1.7 (male) and 2.7 (female) mg/kg/day, based on changes in liver, kidney and thymus weights. The NOEL for reproductive toxicity was  $\geq 180$  ppm, based on an absence of significant effects on reproduction parameters at the HDT.

In a second 2-generation reproduction study, which was unacceptable because of the absence of necropsy and histopathology data, very similar effects were observed (Becker *et al.*, 1986). An additional effect reported in this study was a decrease in absolute and relative spleen weight in females at 180 ppm, as well as an increased activity of alkaline phosphatase in offspring from all matings.

## G. DEVELOPMENTAL TOXICITY

### Gavage-Rat

In a study using Wistar rats, which was acceptable according to FIFRA guidelines, (Baeder *et al.*, 1982a) technical fenoxaprop-ethyl (93.0% pure) was given by daily oral gavage to groups of 20 dams per dosage, on gestation days 7-16 at dosages of 0, 10, 32 or 100 mg/kg/day (Table 7). Signs of maternal toxicity, at the highest dose only, included a slight decrease in food consumption and weight gain compared with controls and piloerection. Also, although not statistically significant by Fisher's exact test ( $p < 0.05$ ), there was a 10% rate of abortion at the highest dosage, compared with 0% in the other 3 groups. Fetal effects included reduced weight and length compared with controls. These effects were significant only at 100 mg/kg/day. An increased incidence of skeletal anomalies was also observed, reflecting weak ossification at three sites, at the highest dose. Similarly, increased visceral anomalies, such as distension of the renal pelvis, were observed at the HDT. The maternal and developmental NOELs were 32 mg/kg/day.

Similar effects were observed in a second study, at identical dosages, using Charles River CD (SD) rats, which was unacceptable to DPR because of inadequate analysis of the dosing solutions (James *et al.*, 1983). However, this report showed dose-dependent increases in both skeletal and visceral fetal anomalies (Table 8). The increased frequency of visceral anomalies occurred at both 32 ( $p < 0.01$ ) and 100 ( $p < 0.001$ ) mg/kg/day and generally reflected an increased incidence of dilation of the kidneys and ureters. Skeletal anomalies were

**Table 7 Incidence of developmental effects in Wistar rats after treatment with fenoxaprop-ethyl during gestation.**

Parameter	Dosage (mg/kg/d)			
	Vehicle control	10	32	100
early abortion, fetal death	0/20	0/20	0/20	4/40
mean fetal wt., $\pm$ s.d.	3.34 $\pm$ .37 g (n = 232)	3.26 $\pm$ .16 g (241)	3.25 $\pm$ .20 g (232)	2.97 $\pm$ .20 <sup>***a</sup> (204)
mean fetal length, $\pm$ s.d.	3.61 $\pm$ .12 cm	3.60 $\pm$ .06 cm	3.59 $\pm$ .13 cm	3.52 $\pm$ .11 <sup>a</sup>
skeletal anomalies <sup>b</sup>	1/120	3/127	5/120	15/106 <sup>***c</sup>
renal pelvis distended <sup>b</sup>	0/120	2/127	3/120	11/106 <sup>***c</sup>

\* significantly different from control at  $p < 0.05$

\*\*\* significantly different from control at  $p < 0.001$

a/ Student's t test, unpaired.

b/ number/total number of fetuses examined.

c/ Fisher's exact test

**Table 8 Incidence of developmental effects in Charles River (SD-derived) rats after treatment with fenoxaprop-ethyl during gestation.**

Parameter	Dosage (mg/kg/d)			
	Vehicle control	10	32	100
mean maternal liver wt. relative body weight	14.95 g	14.84 g	15.29 g	16.41 g <sup>**a</sup>
mean fetal wt.	3.40 g	3.41 g	3.41 g	3.05 g <sup>***b</sup>
<u>visceral anomalies</u>				
number fetuses/ total	5/114	9/131	18/111 <sup>***c</sup>	21/116 <sup>***c</sup>
number litters/ total	3/24	6/24	12/24 <sup>**c</sup>	16/24 <sup>***c</sup>
mean % fetuses per litter	4.2%	7.5%	16% <sup>**b</sup>	18.3% <sup>***b</sup>
<u>skeletal anomalies</u>				
number fetuses/ total	6/113	21/135 <sup>**c</sup>	17/111 <sup>*c</sup>	31/119 <sup>***c</sup>
number litters/ total	6/24	14/24 <sup>*c</sup>	11/24	19/24 <sup>***c</sup>
mean % fetuses per litter	8.8%	16.9%	14.6%	24.9% <sup>***b</sup>

\* significantly different from control at  $p < 0.05$

\*\* significantly different from control at  $p < 0.01$

\*\*\* significantly different from control at  $p < 0.001$

a/ Williams' test.

b/ Kruskal-Wallis test.

c/ Fisher's exact test

also significantly more common than in the control group, at all three doses, regardless of whether the fetus or the litter was the experimental unit. These anomalies were manifestations of reduced ossification, principally affecting the cranial centers and the sacrocaudal vertebral arches. Reduced fetal body weight was also apparent at the high dose. Although the toxicological significance of an increased number of either skeletal or visceral anomalies may be equivocal, the presence of both types simultaneously increases the biological significance of these findings. Thus, in this study, the maternal NOEL was  $\geq 100$  mg/kg/day, because an increased liver weight alone is not considered adverse, and the developmental NOEL, 10 mg/kg/day, based on increased skeletal and visceral anomalies. Because the NOEL for developmental toxicity is lower than that for maternal toxicity, it is unlikely that the fetal anomalies were a direct result of maternal toxicity.

In a third study, which was also unacceptable to DPR because of the lack of analytical data for the dosing solutions, (Baeder *et al.*, 1986), technical material was given at the same dosages to groups of 20 to 22 pregnant Wistar rats by gavage. Maternal and developmental NOELs were considered to be  $\geq 100$  mg/kg, the HDT.

#### **Dermal-Rat**

Technical fenoxaprop-ethyl (HOE 33171; 96.5% pure) was administered dermally on days 6 to 15 of gestation at dosages of 0, 100, 300 or 1000 mg/kg/day to groups of 25 pregnant Wistar rats per group for 6 hours/day (Leist *et al.*, 1984a). Only local effects close to the site of application were observed i.e. slight erythema. No test-article differences were found in the mean number of implantations, resorptions, fetal weight or evidence of embryonic/teratogenic potential. The maternal and developmental NOEL was  $\geq 1000$  mg/kg/day. Because of inadequate analysis of dosing solutions, this study is unacceptable to DPR.

#### **Gavage-Rabbit**

In two experiments which, when considered together, constitute an acceptable study, fenoxaprop-ethyl (HOE 33171; 93% and 96.2% pure) was administered by gavage on days 7 to 19 of pregnancy at dosages of 0, 12.5, 50 or 200 mg/kg/day (Baeder *et al.*, 1982b) and 0, 2, 10 or 50 mg/kg/day (Baeder *et al.*, 1983) to 15 Himalayan rabbits per treatment group. The maternal NOEL was established at  $\geq 50$  mg/kg/day in the two studies, based on increased abortions and reduced food consumption during the first 3 weeks of the first study at 200 mg/kg/day (both significant at  $p < 0.05$ ) and no significant effects at 50 mg/kg/day.

The developmental NOEL in the first study was established at 50 mg/kg/day, based on growth retardation, reduced survival rate, diaphragmatic hernias (8% vs. 0 to 1.3%, control) and increased incidence of a 13th. rib (41% vs. 0 to 10%, control) at 200 mg/kg/day. In the second study the NOEL was  $\geq 50$  mg/kg/day, due to there being no effects at the HDT.

#### **Dermal-Rabbit**

Technical fenoxaprop-ethyl (HOE 33171; 96.5% pure) was administered dermally for 6 hours/day on days 6 to 18 of pregnancy at dosages of 0, 100, 300 or 1000 mg/kg/day to 16 dams per treatment group (Leist *et al.*, 1984b). The developmental and maternal NOELs were  $\geq 1000$  mg/kg/day since there were no effects at the HDT. This study was unacceptable due to the lack of dose solution analysis.

### Gavage-Mouse

Technical fenoxaprop-ethyl (HOE 33171; 96.2% pure) was administered by gavage on days 6 to 15 of pregnancy at dosages of 0, 2, 10 or 50 mg/kg/day to 30 dams per treatment group (James *et al.*, 1985). No treatment-related differences in reproductive parameters were noted. The only maternal effect was a 26% increase ( $p < 0.01$ ) in absolute liver weight at the highest dosage, which alone, is not considered adverse. The NOEL for developmental and maternal effects was  $\geq 50$  mg/kg/day. This study was considered unacceptable because of the lack of analysis of dosing solutions.

### Gavage-Monkey

Technical fenoxaprop-ethyl (HOE 33171; 96.2% pure) was administered by gavage on days 20 to 50 of gestation at dosages of 10 or 50 mg/kg/day to 23 and 11, respectively, pregnant Cynomolgus monkeys (Osterburg, 1984). No untreated, concurrent controls were run and for this reason, historical control data from the laboratory conducting the study were obtained. The results of this supplemental study are summarized in Table 9. No adverse developmental effects were observed, even at the highest dosage, thus giving a developmental NOEL of  $\geq 50$  mg/kg/day. The NOEL for maternal toxicity was initially considered to be  $< 10$  mg/kg/day, based on 24% abortions at this dosage level. However, historical control data show a range of 0 to 40% for abortions, making this measure of maternal toxicity uncertain. Although there was a trend, suggesting a possible dose-dependency for rate of abortions, there was no significant difference between the historical control and dosed monkeys using Fisher's exact test ( $p=0.3$ ). Maternal mortality (45%) was reported, with the first death occurring after the 3<sup>rd</sup> daily administration at 50 mg/kg/day. Necropsies showed nephritis, tubular nephrosis, enteritis with hemorrhagic ulcers in the stomach, chronic nephropathy with hemorrhagic ulcers in the stomach and pneumonia with slight enteritis, in the 5 individuals which died. Because diarrhea and reduced food intake at 10 mg/kg/day were probably a result of sesame oil, which was used as vehicle for intubations, the maternal NOEL in this study was considered to be 10 mg/kg/day.

**Table 9** Incidence of effects in Cynomolgus monkeys after treatment with fenoxaprop-ethyl during gestation (Osterburg, 1984).

Effect	Dosage (mg/kg/day)		Historical control <sup>a</sup>
	10	50	
Maternal death	0/21 (0%)	5/11 (45%)	not available
Abortions	5/21 (24%)	3/11 (27%)	mean 18% <sup>b</sup> range 0-40%

a/ supplemental information provided by registrant owing to the absence of concurrent controls.

b/ n=15 studies for abortions.

A summary of the (9) developmental toxicity studies is presented in Table 10, below. Except for the (two) studies noted, the maternal and developmental NOEL values were the same.

**Table 10 Summary of Developmental Toxicity studies with fenoxaprop-ethyl**

SPECIES/STUDY	NOEL Developmental (mg/kg/day)	Reference
Rat - gavage	32 <sup>a</sup>	Baeder <i>et al.</i> , 1982a
Rat - gavage	10 <sup>b,c</sup>	James <i>et al.</i> , 1983 <sup>d</sup>
Rat - gavage	≥ 100	Baeder <i>et al.</i> , 1986 <sup>d</sup>
Rat - dermal	≥ 1,000	Leist <i>et al.</i> , 1984a <sup>d</sup>
Rabbit - gavage	50 <sup>a</sup>	Baeder <i>et al.</i> , 1982b <sup>e</sup>
Rabbit - gavage	≥ 50	Baeder <i>et al.</i> , 1983 <sup>e</sup>
Rabbit - dermal	≥ 1,000	Leist <i>et al.</i> , 1984b <sup>d</sup>
Mouse - gavage	≥ 50	James <i>et al.</i> , 1985 <sup>d</sup>
Monkey - gavage	≥ 50 <sup>f</sup>	Osterburg, 1984 <sup>g</sup>

a/ reduced fetal weight

b/ increased skeletal and visceral anomalies

c/ maternal NOEL > fetal NOEL.

d/ unacceptable: lack of analysis data on dosing solutions

e/ when combined, these studies satisfy FIFRA requirements

f/ maternal NOEL was 10 mg/kg/day, based on maternal mortality at 50 mg/kg/day.

g/ supplementary

## H. NEUROTOXICITY

Delayed neurotoxicity studies are not required under current FIFRA study guidelines.

## I. SPECIAL TOXICITY STUDIES: HEPATOTOXICITY

### Dietary-Rat

A supplemental study was undertaken to identify any potential hepatotoxicity in terms of abnormal liver histology or biochemistry in the rat, strain WISKf (SPF71) (Ebert *et al.*, 1982a). Groups of 15 rats per dose were fed diets containing fenoxaprop-ethyl (HOE 33171; >96% pure) at 0, 0.2 or 2.0 ppm for 60 days. These were equivalent to dosages of 0, 0.2 or 1.9 mg/kg/day (males) and 0, 0.2 or 2.0 mg/kg/day (females).

Groups of 5/sex/dose were sacrificed at the conclusion of this period and after 14 and 28 days recovery. There were no abnormal effects observed during the study: behavior, general health, body weight gain, food and water consumption, absolute and relative liver weights, peroxisomal proliferation, glutathione depletion and enzyme induction (catalase, aminopyrine N-demethylase and cytochrome c reductase) were all similar to control values. The NOEL was therefore  $\geq 1.9$  (male) and  $\geq 2.0$  (female) mg/kg/day, owing to no effect at the highest dose tested.

### Dietary-Mouse

A similar supplemental study to the rat hepatotoxicity one was conducted using the mouse, strain N6G.Kf (SPF71) (Ebert *et al.*, 1982b). The equivalent dosages were 0, 0.4 or 3.6 (male) and 0, 0.4 or 4.0 (female) mg/kg/day. In this experiment some abnormalities were noted: at the end of the treatment period, both sexes showed reduced levels of glutathione, 80 to 85% of control ( $p < 0.05$ ) and in males, an increased aminase activity to 150% of control ( $p < 0.05$ ). This enzyme is a marker for peroxisomal proliferation. The activity of cytochrome c reductase, a mitochondrial enzyme, was elevated (slightly) only in low dose females and high dose males ( $p < 0.05$ ) and was therefore of doubtful toxicological significance. There were no statistically significant changes in the activity of aminopyrine N-demethylase, a microsomal xenobiotic-metabolizing enzyme.

Because these biochemical changes were not associated with any macroscopic or microscopic signs of hepatotoxicity and because they disappeared after 28 days recovery period, none of these biochemical effects were considered likely to be of toxicological significance.

## IV RISK ASSESSMENT

### A. HAZARD IDENTIFICATION

Potential adverse effects, primarily reflecting hepatotoxicity, have been identified in acute, subchronic and chronic studies, using various animal species. In acute and sub-chronic studies, hepatomegaly was consistently observed, usually without an effect on body weight. Hepatomegaly following subchronic administration invariably reversed, whenever treatment was discontinued. However, effects on liver biochemistry and histology were sometimes also reported. There were no remarkable effects on liver enzymes which are commonly induced by xenobiotics but alkaline phosphatase increased significantly in subchronic studies in rat, mouse and dog. No studies were completed which investigated the effects of fenoxaprop-ethyl on enzymes involved in lipid metabolism. Inhibitors of acetyl CoA carboxylase, the target enzyme of fenoxaprop, have the capacity, in mammals, to alter blood lipid levels. In the male rat, a reduction ( $p < 0.05$ ) in blood cholesterol and total lipids in a chronic study (**Kramer *et al.*, 1985a**) may be a reflection of inhibition of this enzyme. However, in the female mouse, there was an increase in blood cholesterol at the HDT, in a subchronic study (**Leist *et al.*, 1981**). Male mice in this study showed an increase in total lipids at the two highest doses. It is therefore possible that many of the effects reported in acute, subchronic and chronic studies are manifestations of a compromise of normal liver function. Atrophy of the splenic capsule and thymus in the dog (**Brunk *et al.*, 1980**) and of the thymus in the rat (**Tesh *et al.*, 1985**) could reflect toxicity to the immune system. However, there are insufficient data available from these studies to evaluate the immunocompetence of the animals.

#### Acute Toxicity

Toxic effects following short-term exposure were identified mainly in developmental toxicity studies. Nine such studies were submitted, using four different animal species (**Table 10**). In general, the NOEL values for developmental and maternal toxicity were similar, indicating a lack of a specific developmental effect. In one study, however, (**James *et al.*, 1983**) fetal effects were observed at lower dosages than were maternal effects. These took the form of increased frequencies of skeletal and visceral anomalies, with a LOEL of 32 mg/kg/day and a NOEL of 10 mg/kg/day. The NOEL for maternal toxicity was  $\geq 100$  mg/kg/day, the HDT. This NOEL was based on the lack of significant toxicological effects at this dosage.

In a developmental toxicity study using the *Cynomolgus* monkey, a developmental NOEL of  $\geq 50$  mg/kg/day was determined, along with a maternal NOEL of 10 mg/kg/day (**Osterburg, 1984**). A high rate of abortions was reported, at both doses, and 45% maternal mortality at 50 mg/kg/day (0% at 10 mg/kg/day). There was no concurrent control, but the rates of abortions, although high, were within the range of historical controls. Because the first mortality was observed after only eight doses, this can be considered an acute, treatment-related effect with a maternal LOEL of 50 mg/kg/day and a NOEL of 10 mg/kg/day.

In addition, U.S. EPA considered the rabbit NOEL also to be 10 mg/kg/day (**Baeder *et al.*, 1983**), based on fetal mortality at 50 mg/kg/day. However, in reviewing this study, together with **Baeder *et al.*, 1982b**, a NOEL of 50 mg/kg/day was determined for maternal and developmental toxicity, on the basis of significantly increased abortions and fetal anomalies/growth retardation occurring only at 200 mg/kg/day, the HDT.

The NOEL of 10 mg/kg/day, based on increased rat fetal anomalies and mortality in pregnant *Cynomolgus* monkeys was, therefore, used to calculate margins of safety for acute dietary and short-term occupational exposures to fenoxaprop-ethyl.

## Subchronic

Subchronic toxicity by dietary exposure to fenoxaprop-ethyl was expressed in a 30-day mouse study as liver toxicity *i.e.* increased absolute and relative weight with abnormal histopathology, with a LOEL of 3.5 mg/kg/day and a NOEL of 1.9 mg/kg/day in females (Leist *et al.*, 1981). This NOEL was used in the calculation of MOS values for seasonal worker exposure because 30 days is close to the duration of the spraying season for rice.

A feature of the subchronic studies was that, whenever reported, treatment-related effects disappeared with time following the discontinuation of treatment. Such reversibility occurred after a 4-week recovery period in 3-month rat (Donaubauer *et al.*, 1981), 3-month dog (Brunk *et al.*, 1981), 21-day rat (Ullmann, 1984a) and 6-week rat studies (Leist *et al.*, 1984c).

## Chronic Toxicity

Potentially adverse, chronic effects were identified in 2-year feeding studies in rat, mouse and dog. Effects on organ weights were observed in rodents, along with calcareous deposits in the renal pelvis and effects on adrenal histology. The female rat and mouse had 2-year NOEL values of 2.0 and 1.6 mg/kg/day respectively. The lowest chronic NOEL was observed in the 2-year dog study where reduced body weight gain, reduced body weight and increased relative liver weight were reported, with a NOEL of 1.1 mg/kg/day for the male and 0.9 mg/kg/day for the female. Analogous to the reversal of effects following treatment discontinuation in subchronic studies, adaptability was often noted in chronic studies with the continued consumption of fenoxaprop-ethyl. For example, reversible chronic interstitial pyelonephritis, detected in 50% of males in a 3-month dog study at 75 ppm (Brunk *et al.*, 1981) was not observed (at 80 ppm in 1-year and 2-year studies (Brunk *et al.*, 1984; 1985). A NOEL value of 0.9 mg/kg/day was used to calculate a MOS for chronic dietary exposure to fenoxaprop-ethyl.

Two definitive multi-generation rat reproduction studies were conducted for fenoxaprop-ethyl, yielding very similar results (Tesh *et al.*, 1985; Becker *et al.*, 1986). The only statistically significant, dose-related effects occurring in these studies were on organ weights: increased absolute and relative liver weights in adults and offspring; increased absolute and relative kidney weights in offspring; decreased absolute and relative thymus weights in offspring. In one of these studies there was also a consistent decrease in spleen weight in females ( $p < 0.05$ ). The LOEL for these effects was 180 ppm and the adult and developmental NOEL was 50 ppm, equivalent to 1.7 mg/kg/day. U.S. EPA established a maternal NOEL of 5 ppm, based on reduced blood lead levels in parents and reduced body weight in offspring. This was the basis for the U.S. EPA Reference Dose (RfD), the equivalent dosage (0.25 mg/kg/day) being divided by a 100 uncertainty factor, giving 0.0025 mg/kg/day. However, the toxicological relevance of the effect on lipid levels is unclear to DPR, because of the lack of dose-dependency. Furthermore, although total cholesterol and total lipid levels were slightly reduced in parents (F<sub>0</sub>F<sub>1</sub>) at 180 ppm, these levels were increased in offspring (F<sub>1</sub>B). Significantly reduced body weight gain in pups only occurred at 180 ppm.

## Oncogenicity

There was no evidence of oncogenicity in chronic studies in rat, mouse and dog (Kramer *et al.*, 1984; Kramer *et al.*, 1985 a,b; Brunk & Kramer, 1985).

## B. EXPOSURE ASSESSMENT

### Occupational Exposure

Absorbed daily dosage (ADD) and seasonal average daily dosage (SADD) were estimated for aerial application using a surrogate study of worker exposure to the rice herbicide Londax.<sup>®</sup> For ground application, a surrogate study used a WHIP<sup>®</sup> occupational exposure study on soybean (**Volume II**). Because of the strictly seasonal use of WHIP<sup>®</sup> on rice, the reversal of sub-chronic toxicity following a recovery period (**Section IV-A**), and the lack of oncogenicity in the long-term studies, calculations of annual (AADD) and lifetime (LADD) worker exposure were considered inappropriate. Furthermore, only one analog of WHIP,<sup>®</sup> fluazifop-butyl, is presently registered in California, for soybean (a minor crop) and cotton.

#### Mixer/Loader

The exposure of a mixer-loader involved in aerial application to rice of WHIP<sup>®</sup> resulted in an estimated mean absorbed daily dosage of fenoxaprop-ethyl of  $2.9 \pm 1.6$   $\mu\text{g}/\text{kg}/\text{day}$  (ADD) and a mean seasonal exposure of 1.2  $\mu\text{g}/\text{kg}/\text{day}$  (SADD) (**Table 11**).

#### Applicator

For a pilot applying WHIP<sup>®</sup> to rice, the equivalent means of absorbed daily dosages of fenoxaprop-ethyl were  $52 \pm 42$   $\mu\text{g}/\text{kg}/\text{day}$  (ADD) and 22  $\mu\text{g}/\text{kg}/\text{day}$  (SADD) (**Table 11**).

Ground application activities resulted in analogous ranges of dosages of 1.0 to 22  $\mu\text{g}/\text{kg}/\text{day}$  (ADD) and 0.29 to 6.3  $\mu\text{g}/\text{kg}/\text{day}$  (SADD) (**Table 11**).

#### Flagger

The exposure of a flagger involved in aerial application to rice resulted in an estimated mean absorbed daily dosages of  $43 \pm 40$   $\mu\text{g}/\text{kg}/\text{day}$  (ADD) and seasonal exposure of 18  $\mu\text{g}/\text{kg}/\text{day}$  (SADD) (**Table 11**).

**Table 11 Worker exposure to fenoxaprop-ethyl.<sup>a</sup>**

WORKER	ADD <sup>b</sup> $\mu\text{g}/\text{kg}/\text{day}^d$	SADD <sup>c,e</sup> $\mu\text{g}/\text{kg}/\text{day}^d$
Pilot <sup>f</sup> (n=3)	$52 \pm 42$ (10) <sup>g</sup>	22 <sup>h</sup>
Mixer-Loader <sup>f</sup> (n=3)	$2.9 \pm 1.6$ (10)	1.2 <sup>h</sup>
Flagger <sup>f</sup> (n=3)	$43 \pm 40$ (10)	18 <sup>h</sup>
Ground Application <sup>j</sup> (n=3)	1.0 to 22 (3)	0.29 to 6.3 <sup>i</sup>

a/ see **Volume II** for calculations of worker exposure, based on surrogate data from a Londax<sup>®</sup> study.

b/ ADD = Absorbed daily dosage; c/ SADD = Seasonal average daily dosage.

d/ Mean ADD or SADD  $\pm$  S.D., aerial; range for ground applicators.

e/ Application season = 35 days (25 - 60 after planting).

f/ Londax<sup>®</sup> study conducted at three sites, over 10 days and a total of 80 loads.

g/ Number of person/exposure days.

h/ Application days = 15 (aerial) per season; i/ Application days = 10 (ground) per season.

j/ Whip<sup>®</sup> study conducted with 3 persons, on 1 day with a total of 20 loads.

## Dietary Exposure

### **Residue Data**

Human dietary exposure is estimated from consumption and possible residues on commodities with established tolerances for direct food uses. Data on secondary residues in animal tissues are also necessary for estimating human dietary exposures. The sources of residue data include surveillance programs conducted by the DPR and Federal agencies, field trials, and survey studies by registrants. Residue data obtained from the monitoring programs are preferred for human dietary assessments since they are a more realistic estimate of potential exposure. When residues are at levels higher than established tolerances, they are not utilized in the dietary exposure assessments since they are illegal. In the absence of any measured residues, the DPR dietary exposure assessments utilize surrogate data from the same crop group as defined by U.S. EPA or theoretical residues equal to U.S. EPA tolerances.

The DPR has four major sampling programs: 1) priority pesticide, 2) preharvest monitoring, 3) produce destined for processing, and 4) marketplace surveillance. The U. S. Food and Drug Administration (FDA) has two monitoring programs for determining residues in food: (1) regulatory monitoring and (2) total diet study. The former program, like the DPR marketplace surveillance program, examines produce and processed foods at the wholesale and retail levels of trade, as well as imported produce at the point of entry. The total diet study determines residues in foods after they have been prepared for consumption. The National Residue Program of the U. S. Department of Agriculture (USDA) 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.

The residue data for fenoxaprop-ethyl (**Table 12**) used for dietary exposure assessment were obtained from extensive field trials performed by the registrant. In 34 trials on rice, conducted over a 5-year period on 12 different varieties, the combined residues (fenoxaprop-ethyl, fenoxaprop and benzoxazolone metabolite) were < 0.02 ppm, the limit of detection (LOD). The rates of application were 0.2 and 0.4 lb a.i./A, compared with the maximum label rates of 0.2 lb/application and 0.3 lb/season, and the pre-harvest interval (PHI) was 57 to 131 days. The studies used both ground (n=22) and aerial (n=12) applications. Residues were found to dissipate rapidly; within 30 days of application, the combined residues were below the tolerance for rice *i.e.* 0.05 ppm, the limit of quantification (LOQ), lending support to the established PHI of 80 days.

The residue levels for cattle and milk were obtained from a cattle metabolism study conducted using fenoxaprop-ethyl and its benzoxazolone metabolite (**Hoechst, 1987**). These were administered in the diet at concentrations equivalent to 0.2, 0.6 and 2 ppm of each chemical for 4 weeks, resulting in residues in meat and milk below 0.01 ppm (LOD). Residue data were not made available by the registrants for peanuts, soybeans, wheat and other animal products for which tolerances have been granted by U.S. EPA in **40 CFR 180.430** or for barley, for which a temporary tolerance is valid until 4-10-1994 (**Table 12**).

**Table 12 Fenoxaprop-ethyl residue database from registrant monitoring.<sup>a</sup>**

Commodity	Tolerance (ppm) <sup>b</sup>	Studies (n)	RESIDUE	
			Highest, ppm	Mean, ppm
Rice grain, straw	0.05	34 <sup>c</sup>	< 0.02	< 0.02
Rice, processed <sup>d</sup>	0.05	4 <sup>e</sup>	< 0.02	< 0.02
Peanuts	0.05	-	-	-
Soybeans	0.05	-	-	-
Wheat, grain	0.05	-	-	-
straw	0.5	-	-	-
Cottonseed	0.05	-	-	-
Barley <sup>f</sup>	0.05	-	-	-
Cattle	0.05	1 <sup>g</sup>	≤ 0.01	≤ 0.01
Goats	0.05	-	-	-
Hogs	0.05	-	-	-
Horses	0.05	-	-	-
Sheep	0.05	-	-	-
Milk	0.02	1 <sup>g</sup>	< 0.01	< 0.01

a/ **Hoechst Field Trials: Rice 1983-5; 1985a,b; 1987.**

b/ **Federal Register 40 CFR 180.430.**

c/ 34 individual field trials conducted in AR, CA, LA, MS and TX at 0.2 and 0.4 lb./A.

d/ grain, straw, hulls, bran and milled grain (polished rice).

e/ 4 field trials in LA, MS, MO and TX at 0.2 and 0.4 lb./A. "**Fenoxaprop-ethyl: Magnitude of the Residue - Processed Food/Feed.**" Hoechst-Roussel report; Record #115960, 1992.

f/ Temporary tolerance which expires on 4-10-1994.

g/ "**HOE-033171 - Ruminant Feeding study**" Hoechst Study No. A36705, 10/19/87.

### Acute Exposure

Because this pesticide has not been used previously in California, residues of fenoxaprop-ethyl and its degradates have not been monitored by DPR. FDA has monitored several crops in other states for fenoxaprop-ethyl residues since 1989, without detecting any residues. Data from field trials conducted by the registrants confirm the lack of persistence of fenoxaprop-ethyl residues in rice (**Hoechst Field Trials: Rice 1983-5; 1985a,b; 1987**). These trials indicated no detectable residues in rice; thus the LOD of 0.02 ppm was used as a default value for assessing acute, dietary exposure (**Table 12**).

## Chronic Exposure

Because the surveillance data did not indicate any detectable residues in rice (**Table 12**), 50% of the LOD of 0.02 ppm, *i.e.* 0.01 ppm, was used as a default value for assessing chronic dietary exposure.

## Dietary Assessment

### Acute Exposure

Estimates of potential acute dietary exposure used the highest measured residue values at or below the tolerance for each commodity. These were 0.01 ppm (milk and cattle), 0.02 ppm (rice) and 0.05 ppm (peanuts, soybeans, wheat grain, cottonseed, goats, hogs, horses, sheep). 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 or increase the residue concentration, and (4) all foods that are consumed will contain the highest reported residue. The third assumption is not contradicted by the results of the four processed rice residue studies: no detectable residues were recovered (<0.02 ppm), the same as for raw rice (**Table 12**).

Acute dietary exposure analyses were conducted using the Exposure-4™ software program developed by Technical Assessment Systems, Inc. (TAS). The Exposure-4™ program estimates the distribution of user-day (consumer-day) exposure for the overall U.S. population and specific population subgroups (TAS, 1992a). A user-day is any day in which at least one food from the specific commodity list is consumed. The consumption analysis uses individual food consumption data as reported in the 1987-88 USDA Nationwide Food Consumption Survey (USDA, 1987-88).

Based on the 95<sup>th</sup> percentile of user-day exposures for all specific population subgroups, the potential acute dietary exposure of fenoxaprop-ethyl from the labeled use on rice ranged from 0.03 to 0.2 µg/kg/day (**Table 13**). Pregnant, non-nursing females of 13+ yrs. had the lowest potential acute dietary exposure to fenoxaprop-ethyl and non-nursing infants had the highest potential exposure. The complete dietary exposure analysis is presented in Appendix B.

**Table 13 Potential acute dietary exposure to fenoxaprop-ethyl residues in rice and in all commodities with U.S. EPA tolerances.**

Population subgroup	95 <sup>th</sup> percentile of dietary exposure ( $\mu\text{g}/\text{kg}\text{-day}$ )	
	RICE <sup>a,c</sup>	ALL COMMODITIES <sup>b,d</sup>
US Pop. all seasons	0.051	0.590
Western Region	0.049	0.589
Hispanics	0.075	0.610
Non-Hispanic Whites	0.038	0.584
Non-Hispanic Blacks	0.064	0.620
Non-Hispanic Other	0.144	0.627
Infants (nursing)	0.064	0.355
Infants (non-nursing)	0.233 <sup>e</sup>	1.05
Children (1-6 yrs)	0.091	1.09
Children (7-12 yrs)	0.074	0.721
Females (13-19 yrs) (not pregnant, not nursing)	0.043	0.382
Females (13+ yrs) (pregnant, not nursing)	0.029	0.289
Females (13+ yrs) (nursing)	0.048	0.326
Females (20+ yrs) (not pregnant, not nursing)	0.039	0.281
Males (13-19 yrs)	0.051	0.429
Males (20+ yrs)	0.039	0.329
Seniors (55+ yrs)	0.030	0.281

<sup>a</sup> 0.02 ppm, LOD.

<sup>b</sup> Residues = LOD or tolerance *i.e.* 0.01 ppm for beef, veal and milk; 0.02 ppm for rice; 0.05 ppm for soybean, wheat, cottonseed, peanut, barley, goat, sheep, pork.

<sup>c</sup> based on 49% of person days being user-days; range 18% to 49%.

a user-day is any day on which at least one food item from the specific commodity is consumed.

<sup>d</sup> based on 100% of person days being user-days; range 98.2% to 100%.

<sup>e</sup> 49% of person days are user-days for non-nursing infants.

Potential acute dietary exposure was also determined for all commodities with U.S. EPA tolerances, using the Exposure-4<sup>m</sup> program (Table 13). Although rice is the only crop for which a tolerance is being applied in California, other crops can be treated with fenoxaprop-ethyl in other parts of the USA and legally imported and sold in California, provided that the residues are not above the tolerance. Based on the 95<sup>th</sup> percentile of user-day exposures for all specific population subgroups, the potential acute dietary exposure to fenoxaprop-ethyl from all labeled uses ranged from 0.28  $\mu\text{g}/\text{kg}/\text{day}$  for non-pregnant, non-nursing females of 20+ yrs., to 1.09  $\mu\text{g}/\text{kg}/\text{day}$ , for children (1-6 yrs.). The complete dietary exposure is presented in Appendix B.

## Chronic Exposure

Estimates of potential chronic dietary exposure used the average of measured and "below detection limit" residue values for rice. All measured residues were below the LOD. The default procedure assumed that "below detection limit" residues were equal to one-half (50%) of the LOD for rice (0.01 ppm). The following assumptions were used to estimate potential chronic dietary exposures from measured residues: 1) the residue level does not change over time, 2) residues are not reduced by washing the RAC, 3) processing of the RACs into various food forms does not reduce or increase the residue concentration, 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 (annual) dietary exposure from rice residues was calculated using the Exposure-1™ software program of TAS, Inc. (TAS, 1992b). The food consumption data for the chronic analysis was also based on the 1987-88 USDA Nationwide Food Consumption Survey (USDA, 1987-88). The program estimates the annual average exposure for all members of a designated population subgroup (Table 14).

The mean potential chronic dietary exposure to fenoxaprop-ethyl for all population subgroups, consuming only rice, ranged from 0.001 to 0.012  $\mu\text{g}/\text{kg}/\text{day}$ . The population subgroup of non-nursing infants had the highest potential exposure. The complete chronic dietary exposure analysis is presented in Appendix B.

Potential chronic (annual) dietary exposure also was calculated for all commodities with U.S. EPA tolerances, to allow for their possible legal importation into California, using the Exposure-1™ software program developed by TAS, Inc. (Table 14). The residue levels used in this calculation were 50% of the LOD for those commodities for which residue data were available *i.e.* rice, beef, veal, milk and 50% of the tolerance for those commodities for which residue data were not supplied *i.e.* soybean, wheat, cotton, peanut, goat, sheep, pork. The mean potential chronic dietary exposure for all population subgroups ranged from 0.038 to 0.269  $\mu\text{g}/\text{kg}/\text{day}$ . Nursing infants had the lowest potential exposure and children (1-6 yrs.) had the highest potential exposure. The complete chronic dietary exposure analysis is presented in Appendix B.

## Combined Exposure

### Occupational and Dietary: Acute

For rice containing theoretical residues of 0.02 ppm (LOD) of fenoxaprop-ethyl, the acute dietary exposure estimate was 0.03 to 0.14  $\mu\text{g}/\text{kg}/\text{day}$ , for the population subgroups that may be involved in WHIP® use (Table 13). These quantities would have little effect on the occupational ADD and SADD values for pilots, mixer-loaders or flaggers. For ground application, however, the ADD would increase from the range of 1.0 to 22  $\mu\text{g}/\text{kg}/\text{day}$  to a maximum of 1.1 to 22  $\mu\text{g}/\text{kg}/\text{day}$ . Similarly, the SADD would increase from a range of 0.29 to 6.3 to a maximum of 0.43 to 6.4  $\mu\text{g}/\text{kg}/\text{day}$ . This calculation may overestimate the exposure because it assumes that seasonal dietary consumption of rice will be at the default acute 95<sup>th</sup> percentile dietary level.

### Occupational and Dietary: Chronic

The limited duration of the season of application (35 days) makes annual and lifetime (chronic) worker exposure calculations inappropriate. Moreover, the actual application period is only 15 days (aerial) or 10 days (ground) out of any 35 day season (Volume II) and there is no evidence that the effects from short-term exposure are cumulative and represent a long-term health hazard.

**Table 14 Potential chronic (annual) dietary exposure to fenoxaprop-ethyl residues in rice and in all commodities with U.S. EPA tolerances.**

Population subgroup	Dietary exposure ( $\mu\text{g}/\text{kg}\text{-day}$ )	
	RICE <sup>a</sup>	ALL COMMODITIES <sup>b</sup>
US Pop. all seasons	0.002	0.102
Western Region	0.002	0.104
Hispanics	0.005	0.091
Non-Hispanic Whites	0.001	0.101
Non-Hispanic Blacks	0.003	0.101
Non-Hispanic Other	0.008	0.124
Infants (nursing)	0.003	0.038
Infants (non-nursing)	0.012	0.203
Children (1-6 yrs)	0.003	0.269
Children (7-12 yrs)	0.003	0.172
Females (13-19 yrs) (not pregnant, not nursing)	0.002	0.088
Females (13+ yrs) (pregnant, not nursing)	0.001	0.075
Females (13+ yrs) (nursing)	0.003	0.082
Females (20+ yrs) (not pregnant, not nursing)	0.001	0.088
Males (13-19 yrs)	0.002	0.112
Males (20+)	0.002	0.076

<sup>a/</sup> 50% of LOD, 0.01 ppm.

<sup>b/</sup> Residues = 50% of LOD or tolerance *i.e.* 0.005 ppm for beef, veal and milk; 0.01 ppm for rice; 0.025 ppm for soybean, wheat, cotton, peanut, barley, goat, sheep, pork.

## C. RISK CHARACTERIZATION

### Occupational

The risk characterization process consists of calculating a MOS by dividing the NOEL value for a specific toxicological endpoint (Section IV) by the estimated worker exposure (Table 11). For WHEP® application to rice, the values are as follows:

#### **Mixer-Loader**

The acute MOS, based on the mean ADD, for mixer-loaders for aerial application was 3,400. For workers exposed to the mean ADD plus one standard deviation, the MOS was 1,700 and the mean ADD plus two S.D., gave a MOS of 1,700. The seasonal MOS, based on the mean SADD, was 1,500 (Table 15).

#### **Applicator**

For a pilot, the equivalent MOS values were 190, 110 and 71 (acute) and 36 (seasonal).

Ground application resulted in MOS values which ranged from 450 to 10,000 (acute) and 500 to 6,600 (seasonal) (Table 15).

#### **Flagger**

For a flagger involved in aerial application, MOS values were 230, 120 and 83 (acute) and 110 (seasonal) (Table 15).

**Table 15 Margins of safety from worker exposure to fenoxaprop-ethyl.**

WORKER	ACUTE MOS <sup>a,b</sup>		SEASONAL MOS <sup>c,d</sup>
	MEAN	MEAN + 2S.D.	MEAN
Pilot (n=3)	190 (10) <sup>e</sup>	71 (10)	36
Mixer-Loader (n=3)	3,400 (10)	1,700 (10)	1,500
Flagger (n=3)	230 (10)	83 (10)	110
Ground Application (n=3)	450 - 10,000 (3)		500 - 6,600

a/  $MOS = \frac{NOEL (10 \text{ mg/kg/day})}{\text{Exposure (ADD)}}$

NOEL (acute), from two developmental toxicity studies, based on increased fetal skeletal and visceral anomalies in rat (James *et al.*, 1983) and maternal mortality in *Cyathostegus rosalia* (Osterburg, 1984).

b/ Based on mean ADD and mean + 2 S.D. (aerial); based on ADD range (ground).

The mean plus two standard deviations is roughly equivalent to a 95% confidence interval.

c/  $MOS = \frac{NOEL (1.9 \text{ mg/kg/day})}{\text{Exposure (SADD)}}$

NOEL (subchronic) based on liver toxicity in a 30-day mouse study (Leiss *et al.*, 1981).

d/ Based on mean SADD (aerial); range (ground applicators).

e/ Number of person/exposure days

## Dietary

### **Residue Data**

The residue analysis of fenoxaprop-ethyl combines the parent, free acid and the benzoxazolone metabolite. Rice is the only commodity for which a registration is currently being applied in California. The 34 residue studies conducted by the registrants indicated that the residue in rice was not detectable *i.e.* <0.02 ppm, at 57 to 131 days after application (Table 12). Furthermore, in one of these studies, it was shown that residues were below tolerance (<0.05 ppm) by 30 days (label PHI=80 days). Because the application rate used in these studies included 0.4 lb. a.i./A, which is one-third higher than the maximum application rate of 0.3 lb. a.i./A, the residues in practice, following label directions, are likely to be even lower. It is therefore probable that the default residue value of 0.02 ppm, which was used for assessing the acute dietary exposure, was an overestimate of the residue likely to be present after application following label directions.

The accumulation or concentration of fenoxaprop-ethyl residues in livestock, which have been fed adulterated crops, appears unlikely. The administration of fenoxaprop-ethyl to cattle at levels equivalent to 100% of the diet containing 0.2 ppm, *i.e.* 4X tolerance, resulted in residues at or below 0.01 ppm in meat or milk (Hoechst, 1987). This suggests that the exposure to residues of fenoxaprop-ethyl through secondary accumulation is unlikely.

### **Dietary Assessment**

The margins of safety for potential acute exposure, resulting from the consumption of rice containing 0.02 ppm fenoxaprop-ethyl residues, ranged from 43,000 for non-nursing infants (<1 year) to 338,000 for pregnant, non-nursing females (Table 16). These figures are based on the lowest acute NOEL of 10 mg/kg/day and a user-day exposure of 49%. Acute dietary exposure to fenoxaprop-ethyl residues assuming consumption of all commodities with U.S. EPA tolerances (Table 12), resulted in MOS values ranging from 9,000 to 36,000 (Table 16).

For chronic (annual) exposure, the default residue value of 50% of the LOD (*i.e.* 0.01 ppm) was used for characterizing dietary risk. The MOS values ranged from 77,000 to 1,000,000, with non-nursing infants and pregnant, non-nursing females having the highest and lowest risk, respectively (Table 17). In the event of chronic, dietary exposure to all commodities combined, for which there are U.S. EPA tolerances (Table 12), with 100% user-day exposure, MOS values ranged from 3,400 to 23,700 (Table 17). The two subgroups having the lowest MOS values are children 1-6 yrs. (3,400) and non-nursing infants (4,400). This calculation used residues at 50% of tolerance except for those commodities for which residue data were available *i.e.* rice, beef, veal and milk, where it was considered to be 50% of the LOD.

**Table 16 Margins of safety for potential acute dietary exposure from consuming fenoxazone-ethyl residues in rice and in all commodities with U.S. EPA tolerances.**

Population subgroup	Margin of Safety (MOS) <sup>a,b</sup>	
	RICE <sup>c</sup>	ALL COMMODITIES <sup>d</sup>
US Pop. all seasons	199,000	17.000
Western Region	206,000	17.000
Hispanics	133,000	16.000
Non-Hispanic Whites	267,000	17.000
Non-Hispanic Blacks	157,000	16.000
Non-Hispanic Other	70,000	16.000
Infants (nursing)	156,000	18.000
Infants (non-nursing)	43,000	10.000
Children (1-6 yrs)	111,000	9.000
Children (7-12 yrs)	136,000	14.000
Females (13-19 yrs) (not pregnant, not nursing)	233,000	16.000
Females (13+ yrs) (pregnant, not nursing)	338,000	15.000
Females (13+ yrs) (nursing)	213,000	11.000
Females (20+ yrs) (not pregnant, not nursing)	262,000	16.000
Males (13-19 yrs)	196,000	13.000
Males (20+ yrs)	262,000	10.000
Seniors (55+ yrs)	336,000	16.000

<sup>a/</sup> Residues = LOD or tolerance *i.e.* 0.01 ppm for beef, veal, milk; 0.02 ppm for rice; 1.00 ppm for soybean, wheat, cottonseed, peanut, barley, goat, sheep, pork.

<sup>b/</sup> MOS =  $\frac{\text{NOEL (10 mg/kg-day)}}{\text{Exposure}}$

NOEL of 10 mg/kg/day from two developmental toxicity studies, for skeletal and visceral anomalies in the rat (James *et al.*, 1983) and maternal toxicity in the Cynomolgus monkey (Osterburg, 1984).

<sup>c/</sup> based on 49% of person days being user-days; range 18% to 49%.

a user-day is any day on which at least one food item from the specific commodity is consumed.

<sup>d/</sup> based on 100% of person days being user-days; range 98.2% to 100.0%.

a user-day is any day on which at least one food item from the specific commodity is consumed.

**Table 17 Margins of safety and percentage of U.S. EPA Reference Dose for potential chronic (annual) dietary exposure from consuming fenoxaprop-ethyl residues in rice and in all commodities with U.S. EPA tolerances.**

Population subgroup	Margin of Safety (MOS) <sup>a,b</sup>		% of RfD <sup>c,d</sup>
	RICE	ALL COMMODITIES	
US Pop. all seasons	463,000	8,900	4.1%
Western Region	445,000	8,900	4.1
Hispanics	193,000	9,900	3.6
Non-Hispanic Whites	675,000	8,900	4.1
Non-Hispanic Blacks	262,000	8,900	4.0
Non-Hispanic Other	108,000	7,300	4.9
Infants (nursing)	314,000	23,700	1.5
Infants (non-nursing)	77,000	4,400	8.1
Children (1-6 yrs)	262,000	3,400	10.7
Children (7-12 yrs)	312,000	5,200	6.9
Females (13-19 yrs) (not pregnant, not nursing)	531,000	10,300	3.5
Females (13+ yrs) (pregnant, not nursing)	1,000,000	12,100	3.0
Females (13+ yrs) (nursing)	321,000	11,000	3.3
Females (20+ yrs) (not pregnant, not nursing)	648,000	14,000	2.6
Males (13-19 yrs)	451,000	8,100	4.5
Males (20+)	565,000	11,800	3.1

a/ Residues = 50% of LOD or tolerance *i.e.* 0.005 ppm for beef, veal and milk; 0.01 ppm for rice; 0.025 ppm for soybean, wheat, cotton, peanut, barley, goat, sheep, pork.

b/ MOS =  $\frac{\text{NOEL (0.9 mg/kg-day)}}{\text{Exposure}}$

NOEL of 0.9 mg/kg/day for reduced body weight gain in 2-year dog study (Brunk & Kramer, 1985).

c/ RfD or Reference Dose = 0.0025 mg/kg/day, based on abnormal lipid levels in a 2-generation rat reproduction study, with a NOEL of 0.25 mg/kg/day (U.S. EPA 1985).

d/ % of RfD for all commodities with U.S. EPA tolerance.

### Combined Exposure

#### Occupational and Dietary

The MOS values for combined occupational exposure (acute and seasonal) and dietary exposure to fenoxaprop-ethyl are changed only for ground applicators at the lower end of the occupational exposure range. The acute MOS for combined exposure was decreased from 10,000 (Table 16) to 9,000; the seasonal MOS was reduced from 6,600 to 4,400.

## V RISK APPRAISAL

Risk assessment is the process which is used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance will occur in humans under specific exposure conditions. Every risk assessment has inherent limitations in the application of existing data to estimate the potential risk to human health. Therefore, certain *a priori* assumptions are incorporated into the hazard identification, dose-response assessment and exposure assessment processes. These, in turn, result in uncertainty in the risk characterization, which integrates all of the information in these three processes. Qualitatively, risk assessment for all chemicals has similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the availability and quality of the data and the exposure scenarios being assessed. Varying degrees of uncertainty are involved in the estimation of these two parameters, affecting the accuracy of the risk characterization. Specific areas of uncertainty associated with this risk assessment for fenoxaprop-ethyl are delineated in the following discussion.

Acute toxicity tests measure the effects of a chemical after a single or brief period of exposure. Developmental toxicity studies are a special case in the battery of such tests. Typically, daily dosages are administered to pregnant animals during the period of organogenesis of the fetus. In the absence of data to the contrary, it is assumed that a reported developmental effect can result from a single dose on a particular day during this time period (U.S. EPA, 1991a). Because fenoxaprop-ethyl does not clear the rat or monkey body within 24 hours (Dorn *et al.*, 1984), it is therefore possible that an effect could take place late in the dosing sequence and be the result of an accumulation of chemical above a threshold *i.e.* a single daily dosage may be insufficient to cause the effect. In such a case, the NOEL value in terms of the daily dosage would underestimate the "true" NOEL. The NOEL value which was used to determine the acute MOS values for fenoxaprop-ethyl was derived from two such studies *i.e.* fetal anomalies (rat) and maternal mortality (Cynomolgus monkey) and may, therefore, be an underestimate of the acute NOEL and hence the MOS.

For subchronic toxicity, which has been used to assess the seasonal occupational exposure, another area of uncertainty exists. The toxicological endpoint used for establishing a NOEL was hepatomegaly, combined with dose-dependent histopathological changes in the mouse liver, *i.e.* enlarged hepatic epithelia with relatively large nuclei and dense eosinophilic cytoplasm in the centrilobular region. Qualitatively identical effects were reported in subchronic studies in the rat and dog. Although these effects were demonstrated to be reversible in rat and dog studies, the mouse study did not report reversibility. However, taken together with the rat and dog studies, it is possible that the hepatic effects in the mouse would have reversed with the discontinuation of dosing. Therefore, once again, the experimentally determined NOEL for subchronic effects could be an underestimate of the "true" NOEL and also the MOS.

### Occupational Exposure

Occupational exposure studies using WHIP® on rice were not available to DPR for aerial or ground application. An aerial study using the herbicide Londax® on rice was considered to be a suitable alternative (Volume 2). However, several possible sources of error may exist. For example, quantitative adjustment of exposures based on differences in physicochemical properties and formulations between the two herbicides was not possible. Factors which were adjusted include worker protective clothing, differences in the rate of application and glove penetration. Human dermal penetration data are generally lacking and absorption was assumed to be the same as for the rat, 73%. However, this value is probably an overestimate of dermal penetration since rates in rodents are generally 5 to 10x greater than rates in humans (Feldmann & Maibach, 1974; Wester & Maibach, 1985). Other assumptions, which will tend to have increased the aerial applicator

exposure estimates include the use of maximum label rates, and maximum number of loads per day.

For ground application, an exposure study of workers treating soybean with WHIP® was used as a surrogate. There are possible inaccuracies in modelling the application to rice from the differences in the methods of application to the two crops. This surrogate study also had a small sample size and large variation in the levels of exposure of the individuals involved. Further, only a small proportion of the WHIP® applied to rice in California would be by ground application; the majority will be aerially applied.

### **Daily (acute) Exposure**

For acute exposure, a margin of safety value of 100 or greater is generally considered to be protective of human health when the toxicology (*e.g.* NOEL) is based on animal studies. For aerial application, the mean MOS values were above 100 for pilots, mixer-loaders and flaggers. Similarly, the mean ADD plus one standard deviation gave MOS values above 100. For the mean plus two standard deviations, however, the MOS values for pilots and flaggers were 71 and 83, respectively. For ground applicators, the calculated range of MOS values was above 100.

### **Seasonal Exposure**

For seasonal exposure, a margin of safety value of 100 or greater is generally considered to be protective of human health when the toxicology (*e.g.* NOEL) is based on animal studies. Based on the mean SADD values, the MOS for pilots (86), was below 100, whereas mixer-loaders, flaggers and ground applicators had MOS values above 100.

### **Chronic Exposure**

Because of the limited use season for WHIP® on rice and because of the reversibility of the sub-chronic toxic effects of fenoxaprop-ethyl, the calculation of MOS values associated with annual and lifetime exposure were considered inappropriate.

### **Dietary Exposure**

#### **Acute (Daily)**

The margins of safety from the acute dietary consumption of rice which has been treated with fenoxaprop-ethyl are greater than 100, even at the 95<sup>th</sup> percentile of dietary exposure. The MOS values presented indicate that even the most exposed population subgroups would be protected from residues by the regulations in place *i.e.* a tolerance of 0.05 ppm for the combined residues of fenoxaprop-ethyl and metabolites on rice grain and a PHI of 80 days. Furthermore, the tolerance is unlikely to be approached in practice because it has been shown that even when fenoxaprop-ethyl was applied to rice at rates above the maximum label rate, the combined residues had dissipated to <0.05 ppm within 30 days.

In addition, residues of fenoxaprop-ethyl can be expected to become reduced even further by washing and cooking of rice prior to consumption. Residues have been found not to concentrate during the processing of rice. Furthermore, evidence has been presented which shows that residues do not accumulate in livestock which have been dosed with fenoxaprop-ethyl.

### Chronic (Annual)

The margins of safety from the annual dietary consumption of rice which has been treated with fenoxaprop-ethyl are greater than 100, including population subgroups likely to have the greatest dietary exposure.

### Combined Exposure

Potential dietary exposure will not substantially increase the overall exposure from work-related tasks. Margins of safety for workers are generally greater than 100; estimated dietary exposure will increase potential occupational exposure by less than 1%. For ground applicators, having the lowest anticipated occupational exposure, the potential increase in exposure caused by consuming rice products could increase total exposure by more than 1%, but the MOS values would remain greater than 100.

### Conclusions

A margin of safety of at least 100 is generally considered to be protective of human health when the toxicology endpoints are derived from animal studies. The aerial application of fenoxaprop-ethyl to rice results in MOS values above 100, for acute exposure, with the exception of pilots and flaggers at the 95% confidence interval level of exposure where the MOS values were 71 and 83, respectively. For seasonal exposure, the MOS was above 100 for mixer-loaders and flaggers, but below 100 for pilots, being equal to 86. For the reasons discussed, it is likely that the acute and subchronic NOEL values are underestimated and the occupational exposure overestimated; thus, margins of safety calculated in this document are probably lower than under actual use conditions of fenoxaprop-ethyl on rice. The ground application of fenoxaprop-ethyl to rice results in MOS values above 100, for both acute and seasonal exposure. The dietary consumption of rice containing theoretical levels of fenoxaprop-ethyl, up to and including the tolerance level, resulted in margins of safety above 100 for all consumer subpopulations. Similarly, the potential dietary consumption of other commodities for which tolerances have been established (with U.S. EPA), whether alone or in combination, resulted in margins of safety above 100.

## VI TOLERANCE ASSESSMENT

### Background

A tolerance is the maximum amount of pesticide residue that may remain in or on a food or animal feed (US EPA, 1991). 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 unapproved 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).

The data requirements established by U.S. EPA for tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate studies, (3) toxicology studies which evaluate the hazards to humans, domestic animals, and non-target organisms, (4) product performance such as efficacy, and (5) product chemistry which includes physical-chemical characteristics and analytical methods (Code of Federal Regulations, 1992). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications, and formulations proposed (U.S. EPA, 1982).

Currently, the tolerances set by U.S. EPA are at levels necessary for the maximum application rate and frequency, and are not expected to produce deleterious health effects in humans from chronic dietary exposure (U.S. EPA, 1991b). U.S. EPA uses the Reference Dose (RfD) for non-cancer risks, and negligible level (generally defined as a lifetime probability of additional tumor occurrence at one in a million) for cancer risks as guides to determine the appropriate levels for dietary exposure.

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 subgroups can be calculated from the product of the tolerance and the daily consumption rate.

### Acute Exposure

An acute exposure assessment using the residue level equal to the tolerance was conducted for each individual label-approved commodity. The TAS Exposure-4<sup>™</sup> software program and the USDA National Food Consumption Survey (1987/8) were used in this assessment. The acute tolerance assessment did not address multiple commodities at the tolerance levels since the probability of consuming multiple commodities at the tolerance decreases as the number of commodities included in the assessment increases.

The range of MOS values for rice and other commodities registered by U.S. EPA (**40 CFR 180.430**) is shown in **Table 18**. For rice, residues at tolerance (0.05 ppm) would have a MOS of 16,000 to 130,000 for acute toxicity, based on a NOEL of 10 mg/kg/day. The MOS values for other commodities are even larger, reaching over 1,000,000 for cotton, animal byproducts and sheep fat (**Table 18**). The MOS values for acute dietary exposure to rice at tolerance for various population subgroups are presented in **Table 19**.

**Table 18 Margins of safety for potential acute dietary exposure to commodities with residue values of fenoxaprop-ethyl at tolerance.**

COMMODITY	%USER -DAYS <sup>a</sup>	TOLERANCE ppm	MARGIN OF SAFETY <sup>b</sup> range
RICE	49	0.05	17,000 <sup>c</sup> - 135,000
SOYBEAN	100	0.05	31,000 <sup>c</sup> - 334,000
PEANUT	65	0.05	83,000 <sup>d</sup> - 457,000
WHEAT	100	0.05	26,000 <sup>d</sup> - 93,000
COTTON	97	0.05	632,000 <sup>c,e</sup> - > 1,000,000
MILK	100	0.02	2,200 <sup>c</sup> - 19,000
<u>BEEF + VEAL</u>			
Lean + dried	72	0.05	33,000 <sup>c,d</sup> - 72,000
Fat	95	0.05	140,000 <sup>d</sup> - 410,000
MBYP <sup>j</sup>	1	0.05	300,000 <sup>f</sup> - > 2,000,000
<u>SHEEP</u>			
Lean	4	0.05	29,000 <sup>c,d,g</sup> - 38,000
Fat	4	0.05	130,000 <sup>d,g</sup> - > 1,000,000
MBYP <sup>j</sup>	0	0.05	NO EXPOSURE
<u>HOGS</u>			
Lean	54	0.05	29,000 <sup>h,g,h</sup> - 130,000
Fat	91	0.05	150,000 <sup>d</sup> - 430,000
MBYP <sup>j</sup>	2	0.05	26,000 <sup>d,i</sup> - > 2,000,000
GOATS + HORSES	0	0.05	NO CONSUMPTION IN SURVEY
BARLEY <sup>k</sup>	-	0.05	-

a/ a user-day is any day on which at least one food item from the specific commodity is consumed.

b/ MOS =  $\frac{\text{NOEL (10 mg/kg/day)}}{\text{Exposure}}$

Exposure

NOEL of 10 mg/kg/day from developmental toxicity studies, for skeletal and visceral anomalies in a rat (James *et al.*, 1983) and maternal mortality in a monkey (Osterburg, 1984).

c/ Non-nursing infants

d/ Children, 1-6 yrs.

e/ only 13% of person-days are user-days for non-nursing infants.

f/ Males, 13-19 yrs.; only 0.1% of person-days are user-days.

g/ only 0.2% of person-days are user-days for children, 1-6 yrs.

h/ Nursing infants; only 2.6% of person-days are user-days.

i/ only 0.1% of person-days are user-days for children, 1-6 yrs.

j/ MBYP is meat by-products

k/ MOS calculations were not conducted for barley because it has a temporary tolerance, expiring 4-10-1994.

**Table 19 Potential acute dietary exposure and margins of safety for fenoxaprop-ethyl when residue values on rice are at U.S. EPA tolerance of 0.05 ppm.**

Population subgroup	95 <sup>th</sup> percentile of exposure ( $\mu\text{g}/\text{kg}\text{-day}$ )	MOS <sup>a</sup>
US Pop. all seasons	0.126	79,000
Western Region	0.122	82,000
Hispanics	0.189	53,000
Non-Hispanic Whites	0.094	107,000
Non-Hispanic Blacks	0.160	63,000
Non-Hispanic Other	0.359	28,000
Infants (nursing)	0.160	63,000
Infants (non-nursing)	0.582	17,000
Children (1-6 yrs)	0.225	44,000
Children (7-12 yrs)	0.185	54,000
Females (13-19 yrs)	0.107	93,000
(not pregnant, not nursing)		
Females (13+ yrs)	0.074	135,000
(pregnant, not nursing)		
Females (13+ yrs)	0.118	85,000
(nursing)		
Females (20+ yrs)	0.095	105,000
(not pregnant, not nursing)		
Males (13-19 yrs)	0.128	78,000
Males (20+ yrs)	0.096	105,000
Seniors (55+ yrs)	0.074	135,000

<sup>a/</sup>  $\text{MOS} = \frac{\text{NOEL (10 mg/kg-day)}}{\text{Exposure}}$

### Chronic Exposure

A chronic annual exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels, *i.e.* daily consumption of these commodities for one year at residues equal to the tolerances. Support for this conclusion comes from FDA and DPR (formerly CDFA) pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance for any pesticide (CDFA, 1990-1993).

## VII CONCLUSIONS

### Occupational

A margin of safety of at least 100, whenever it is based on animal toxicity data, is conventionally recommended to protect the population from the toxic effects of a pesticide. Using mean, acute occupational exposure, the estimated margins of safety for the aerial application of fenoxaprop-ethyl to rice were above 100 for all categories of worker. Based on a 95<sup>th</sup> percentile of occupational exposure, the margins of safety for pilots (75) and flaggers (85) were below 100. However, for the reasons discussed in **Section V** (Risk Appraisal), it is likely that the acute NOEL is underestimated and the occupational exposure overestimated; thus, margins of safety calculated in this document are probably lower than under actual use conditions of fenoxaprop-ethyl on rice. For mean seasonal exposure, and using subchronic toxicity data, margins of safety were above 100 for all workers, except pilots (88). This margin of safety may also be an underestimate because of the reasons discussed above (and in **Section V**). For ground applicators, the margins of safety for both acute and seasonal exposure were above 100.

### Dietary

The margins of safety, for potential acute and chronic dietary exposure to fenoxaprop-ethyl residues in rice, were above 100 for all population subgroups. Likewise, margins of safety were above 100, for all population subgroups, for acute or chronic consumption of rice plus other commodities having a tolerance for fenoxaprop-ethyl at residue levels based on default assumptions.

### Combined

The margins of safety for combined occupational and dietary exposure were little different from the exposure estimates for occupational exposure, alone. The only exception was for ground applicators *i.e.* those workers having the lowest estimated occupational exposure. In this case, the margins of safety for combined exposure, although lower than for occupational exposure alone, remained above 100.

### Tolerances

U.S. EPA tolerances for fenoxaprop-ethyl on rice and on all other commodities for which tolerances have been established, whether consumed alone or in combination, provided acute margins of safety for all population subgroups which were above 100.

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## IX APPENDICES

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**APPENDIX A  
TOXICOLOGY SUMMARIES**

**PRODUCT REGISTRATION RECOMMENDATION SHEET**

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TO: James Herota, Registration Specialist  
Pesticide Registration Branch

FROM: Medical Toxicology Branch

Original: 12/23/92  
Revised: 2/18/94

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PRODUCT REGISTRATION RECOMMENDATION SHEET

Formulated Product Name: Whip 1EC Herbicide  
Chemical Code #: 2311 ID #: 135786N  
EPA Reg. #: 8340-23-54382 SB 950 #: New A.I.  
Document #: 51910-002 to -032, and -065  
Company Name: Hoechst-Roussel Agri-Vet Company

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**RECOMMENDATION:**

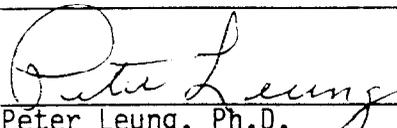
Submitted as a new active ingredient Section 3 registration request.

The data are adequate to make a complete toxicological evaluation of the subject product.

Product label identifies all potential acute hazards indicated by the data reviewed.

Registration is recommended.

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Peter Leung, Ph.D.  
Staff Toxicologist

3/16/94  
Date

  
Gary Patterson, Ph.D.  
Senior Toxicologist

3/16/94  
Date

  
Joyce Gee, Ph.D.  
Senior Toxicologist

3/16/94  
Date

TO: James Herota, Registration Specialist  
Pesticide Registration Branch

FROM: Medical Toxicology Branch

original: 12/23/92  
revised: 2/18/94

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DATA PACKAGE SUMMARY AND RECOMMENDATION SHEET - NEW ACTIVE INGREDIENT

Active Ingredient: Fenoxaprop ethyl  
Formulated Product Name: Whip 1 EC Herbicide  
Formulation (excluding inerts): 12.5% fenoxaprop ethyl, 87.5% inerts  
Chemical Code #: 2311 ID #:135786N  
EPA Reg #: 8340-23-54382 SB 950 #: New A.I.  
Document #'s: 51910 - 002 to -032, and -065  
Company Name: Hoechst-Roussel Agri-Vet Co.

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SUMMARY: ("One-Liners" from each study worksheet or other pertinent information for ongoing review or registration. Attach additional sheets if needed.)

Toxicology data for Whip 1 EC Herbicide and the technical grade active ingredient (TGAI), fenoxaprop ethyl, were submitted to support a Section 3 Registration request.

Whip 1 EC Herbicide is an emulsifiable concentrate formulation containing 1 pound of fenoxaprop ethyl per gallon and is used for postemergence control of annual and perennial grassy weeds in rice. Whip 1 EC does not control broadleaf weeds or sedges.

ACUTE STUDIES - Technical

Toxicity Category

Acute Oral Toxicity LD <sub>50</sub>	Unacceptable and not upgradeable*
Acute Dermal Toxicity LD <sub>50</sub>	Unacceptable and not upgradeable*
Acute Inhalation Toxicity LC <sub>50</sub>	III
Primary Eye Irritation	II
Primary Dermal Irritation	III

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\*See Conclusions

Acute Oral Toxicity

002; 114434; "Acute oral toxicity of HOE 33171 OH AT 203 to the male rat" (Hollander and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 576/79, 10/9/79); 811; HOE 33171 OH AT 203 (TGAI); 1600, 2000, 2250, 2500, and 5000 mg/kg; 10 male rats/dose; 0/10, 0/10, 4/10, 7/10, and 10/10, respectively, died between days 1 and 7 after treatment; clinical signs included passiveness, disequilibrium, squatting, crawling or crouching, bristled hair, blepharophimosis, rhinorrhea; necropsy on animals that died revealed spots and markings on the liver, diffused reddening of the pancreas, petechial hemorrhages in the gastric mucosa (fundic part) and in the duodenum, red-black liquid matter in the entire region of the small intestine; LD50 (M) = 2357 (2240 - 2479) mg/kg; toxicity category not determined; female rats not included in this study; **unacceptable and not upgradeable**; (Leung, 9/18/92).

002; 114435; "Acute oral toxicity of HOE 33171 OH AT 203 to the female rat" (Hollander and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 577/79, 10/2/79); 811; HOE 33171 OH AT 203 (TGAI); 2000, 2500, 3150, 4000, and 5000 mg/kg; 10 female rats/dose; 1/10, 5/10, 9/10, 10/10, 9/10, respectively died between days 1 and 4 after dosing; clinical signs included passiveness, disequilibrium, squatting, crawling or proclivity, bristled hair, blepharophimosis, chromodacryorrhea and increased respiratory rate; necropsy on animals that died revealed bright spots and markings on the liver, diffused reddening of the pancreas, petechial hemorrhages in the gastric mucosa (fundic part) and in the duodenum, red-black liquid matter in the entire region of the small intestine; LD50 (F) = 2500 (2230 - 2780) mg/kg; toxicity category not determined; male rats not included in this study; **unacceptable and not upgradeable**; (Leung, 9/18/92).

002; 114436; "Acute Oral toxicity to the Male Mouse" (Mayer and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 423/79, 7/27/79); 811; HOE 33171 OH AT 203 (TGAI); 3150, 4000, 5000, 5600, and 6300 mg/kg; 10 male mice/dose; 0/10, 4/10, 4/10, 8/10, 10/10, respectively, died within 1 to 5 days after dosing; clinical signs included passiveness, increased respiratory rate, blepharophimosis, disequilibrium, abdominal position, drowsiness, increased lacrimation and jerky respiration; surviving animals were free from clinical symptoms within 48 to 72 hours after dosing; necropsy of animals that had died exhibited extreme filling of the urinary bladder and marking of the hepatic lobules after doses of 6300 mg/kg as well as advanced autolysis in all dosage groups; no abnormal findings were reported in necropsy of surviving animals; LD (M) = 4670 (4180 - 5130) mg/kg; toxicity category not determined; female mice not included in this study; **unacceptable and not upgradeable**; (Leung, 9/18/92).

002; 114437; "Acute Oral Toxicity to the Female Mice" (Mayer and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 424/79, 7/27/79); 811; HOE 33171 OH AT 203 (TGAI); 2500, 3150, 4000, 5000, 5600, and 6300 mg/kg; 10 female mice/dose; 0/10, 0/10, 0/10, 3/10, 8/10, and 6/10, respectively, died within 1 to 7 days after treatment; clinical signs included passiveness, blepharophimosis, increased respiratory rate, disequilibrium, abdominal position, drowsiness, increased lacrimation and jerky respiration; surviving animals free from clinical symptoms within 48 to 72 hours after dosing; necropsy did not reveal any abnormal findings in survivors or in animals that had died; LD50 (F) = 5490 (5010 - 6140) mg/kg; toxicity category not determined; male mice not included in this study; **unacceptable and not upgradeable**; (Leung, 9/21/92).

#### Acute Dermal Toxicity

002; 114438; "Acute Percutaneous toxicity of HOE 33171 OH AT 203 to the Female Rat" (Hollander and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 578/79, 10/2/79); 812; HOE 33171 OH AT 203 (TGAI); 2 g/kg; 24 hour exposure to intact skin site; 6 Wistar rats; all animals survived the study; passivity was observed in all animals; normal behavior and body weight gain were reported 24 hours after dosing; no abnormal findings in necropsy; LD 50 (F) > 2 g/kg; toxicity category not determined; only female rats employed in the study; **unacceptable and not upgradeable**; (Leung, 9/21/92)

Acute Inhalation Toxicity

002; 114439; "Aerosol Inhalation of HOE 33171 (Active Ingredient) in Male and female SPF-Wistar Rats A Four-Hour LC50" (Hollander and Leist, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 352/82, 6/8/82); 813; HOE 33171 OH AT 204 (TGAI); 5% dilution in ethanol/polyglycol (1:1, v/v) to form an aerosol containing 151 and 511 mg HOE 33171/m<sup>3</sup> (analytical); 4 hour nose only exposure; 93.7% - 97.6% of particles < 6 um; 6 rats/sex/dose; one male rat at the high dose died between day 1 and 2 following treatment; necropsy was not possible because of cannibalism; no noteworthy findings were made macroscopically upon dissection of the animals killed at the end of the study; LC50 (M/F) > 511 mg/m<sup>3</sup> or 0.511 mg/l; toxicity category III; **acceptable**; (Leung, 9/24/92).

Primary Eye Irritation

002; 114540; "Irritation to the Rabbit Skin and Eye Mucosa" (Hollander and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 406/79, 7/11/79); 814; HOE 33171 OH AT 203 (TGAI); 100 mg/eye; 6/9 rabbits with unwashed eyes; contralateral right eye remained untreated and served as control; no mortalities reported; unwashed eyes: slight corneal opacity in 4/6 animals and slight to moderate redness, chemosis and discharge in all 6 animals at 1 and 24 hours after administration; by 72 hours grade 1 corneal opacity in 1/6 animals and grade 1 redness and discharge in 2/6 animals; similar findings were observed in the remaining 3 rabbits with washed eyes; toxicity category II; **acceptable**; (Leung, 9/25/92).

Primary Dermal Irritation

002; 114540; "Irritation to the Rabbit Skin and Eye Mucosa" (Hollander and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 406/79, 7/11/79); 815; 6 rabbits; HOE 33171 OH AT 203 (TGAI); 500 mg/skin site; 24 hr exposure at intact skin sites; no mortalities reported; erythema (grade 1-3 in 6/6 rabbits) and edema (grade 1-2 in 6/6 rabbits) at 24 hr, erythema (grade 1-2 in 6/6 rabbits) at 48 hr, and erythema (grade 1 in 1/6 rabbits) at 72 hr; category III; **acceptable**; (Leung, 9/25/92).

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ACUTE STUDIES - Formulation

	Toxicity Category
Acute Oral Toxicity LD <sub>50</sub>	Unacceptable and not upgradeable*
Acute Dermal Toxicity LD <sub>50</sub>	Unacceptable and not upgradeable*
Acute Inhalation Toxicity LC <sub>50</sub>	III
Primary Eye Irritation	II
Primary Dermal Irritation	III

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\*See Conclusions

### Acute Oral Toxicity

032; 114510; "Single-Dose Oral Toxicity Study of HOE 33171 as an Emulsifiable Concentrate 12.5 in Male Rats" (Mayer and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 687/82, 11/2/82); 811; HOE 33171 OH EC 037 (12.5% A.I.); 2000, 3150, 4000, and 5000 mg/kg; 10 male rats/dose; 0/10, 5/10, 7/10, and 10/10, respectively, died between 4 hours and 2 days after treatment; clinical signs included passivity, balance disorders, crawling or crouching stance, hyporeflexia, chromodacryorrhea and noisy breathing; all symptoms had disappeared after 24 hours; necropsy findings showed stomach filled with substance; NOEL (M) = 2000 mg/kg (no effect or mortality at this dose); LD50 (M) = 3310 (2770 - 3740) mg/kg; toxicity category not determined; female rats not included in this study; **unacceptable and not upgradeable**; (Leung, 9/28/92).

032; 114511; "Single-dose Oral Toxicity Study of HOE 33171 as an Emulsifiable Concentrate 12.5 in Female Rats" (Mayer and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, report # 688/82, 11/2/82); 811; HOE 33171 OH EC 037 (12.5% A.I.); 1600, 2500, 2800, 3150, 4000, and 5000 mg/kg; 10 female rats/dose; 0/10, 0/10, 3/10, 6/10, 5/10, and 10/10, respectively, died between 270 minutes and 6 days after dosing; clinical signs included passivity, stupor, staggering gait, balance disorders, hyporeflexia, piloerection, and noisy breathing; all symptoms disappeared after 72 hours; necropsy findings showed distended stomach filled with substance, dark-brown adrenals, full bladder and diffuse reddening of the pancreas; LD50 (F) = 3400 (3050 - 3860) mg/kg; toxicity category not determined; male rats not included in this study; **unacceptable and not upgradeable**; (Leung, 9/28/92).

### Acute Dermal Toxicity

032; 114512; "Single-dose Dermal Toxicity Study of HOE 33171 OH - Emulsifiable Concentrate 12.5 in Male Rats" (Mayer and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 593/82, 10/19/82); 812; HOE 33171 OH EC 037 (12.5% A.I.); 2000 mg/kg; 6 male rats; 24 hour exposure to intact skin site; all animals survived the study; clinical symptoms included drowsiness, stilted gait and hyporeflexia within 180 minutes after application; all symptoms cleared within 24 hours; no remarkable findings evident in necropsy; LD50 (M) > 2000 mg/kg; toxicity category not determined; female rats not included in this study; **unacceptable and not upgradeable**; (Leung, 9/28/92).

032; 114513; "Single-dose Dermal toxicity Study of HOE 33171 OH - Emulsifiable concentrate 12.5 in Female Rats" (Mayer and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 574/82, 10/19/82); 812; HOE 33171 OH EC 037 (12.5% A.I.); 2000 mg/kg; 24 hour exposure to intact skin; 6 female rats; No mortalities were reported; treated animals exhibited drowsiness, stilted gait, and hyporeflexia within 3 hours after dermal application; all symptoms cleared within 24 hours; necropsy revealed no remarkable findings; LD50 (F) > 2000 mg/kg; toxicity category not determined; male rats not included in this study; **unacceptable and not upgradeable**; (Leung, 9/28/92).

### Acute Inhalation Toxicity

032; 114514; "Aerosol Inhalation of HOE 33171 Emulsion concentrate in Male and Female SPF-Wistar Rats" (Hollander and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 26/82, 2/8/82); 813; HOE 33171 OH EC 036 (12.6% A.I.); 1.667, 3.761, 4.143 and 5.452 mg/l (analytical concentration); 79 - 91.6% of particles < 6 um; 6 rats/sex/dose; 4 hour nose only exposure; mortalities: male - 0/6, 4/6, 6/6, and 6/6, respectively, female - 0/6, 2/6, 0/6, and 6/6, respectively; clinical signs included increased salivation, rhinorrhea, sneezing, irregular and spasmodic respiration, balance disorders, ataxia, and hyporeflexia; all symptoms reversed by day 6; necropsy on animals which died during the study exhibited dark red to black pulmonary foci and animals which were killed at the end of study showed no abnormal findings; calculated LC50 (M/F) = 3.920 (3.240 - 4.280) mg/l; category III; **acceptable**; (Leung, 9/29/92).

### Primary Eye Irritation

032; 114515; "Primary Irritation to the Rabbit Skin and Eye Mucosa" (Leist and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 35/82, 2/24/82); 814; HOE 33171 OH EC 036 (12% A.I.); 0.1 ml/eye; 6 rabbits with unwashed eyes, remaining 3 rabbits with washed eyes; right eye of each rabbit served as control; cornea opacity (max. score = 3), iritis (max. score = 2), conjunctivitis (max. scores = 3/redness, 3/chemosis, and 3/discharge) in unwashed eyes; all signs of eye irritation cleared by day 16; similar results were observed for washed eyes except that by day 14 all eye irritations were cleared; category II; **acceptable**; (Leung, 9/29/92).

### Primary Dermal Irritation

032; 114515; "Primary Irritation to the Rabbit Skin and Eye Mucosa" (Leist and Weigand, Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 35/82, 2/24/82); 815; HOE 33171 OH EC 036, (12% A.I.); 0.5 ml/intact skin site; 24 hour exposure; 6 rabbits; erythema (grade 2) and edema (grade 1) were observed up to and including day 7; treated skin area were dry, brittle, scaly, hardened, and showed surface and deeper fissuring; eight days after dermal application, all erythema and edema had disappeared; category III; **acceptable**; (Leung, 9/30/92).

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## SUBCHRONIC STUDIES

### Oral

003; 114441; "Range-Finding Test with HOE 33171 OH AT 203 in a 32-Day Study with SPF-Wistar Rats" (Leist et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 164/80, 6/9/80); HOE 33171 OH AT 203 (TGAI); oral administration of 0 (dietary feed), 80, 315, 1250 and 5000 ppm for 32 days; 10 rats/sex/dose; rats in the 5000 ppm group were killed prematurely on days 8 - 9 due signs of severe intoxication (poor health conditions, refusal of feed, and decreased body weight); elevated alkaline phosphatase at 1250 ppm (122 - 137% of control, p<0.05) in conjunction with increases in absolute and relative liver weights (113 - 151% of control, p<0.05), eosinophilic staining of the cytoplasm and enlarged hepatocytes at 315 and 1250 ppm and liver cell necrosis at 5000 ppm; NOEL (M/F) = 80 ppm (based on signs of liver involvement); **supplemental**; (Leung, 10/2/92).

004; 114442; "Repeated-dose (3 Months) Oral Toxicity Study of the Active Substance HOE 33171 Administered in the Feed to Rats" (Donaubauer et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 695/81, 12/4/81); 821; HOE 33171 OH AT 204 (TGAI); 0, 20, 80 and 320 ppm in daily diet for 3 months; 30 rats/sex/dose; 10 rats/sex/dose group were kept for a 4-week recovery period; all animals survived the study without any abnormal changes in body weight, food and water consumption; "adaptive responses" of the liver to the test compound were exhibited in high dose males; increased absolute liver weight (115% of control,  $p < 0.05$ ) and serum alkaline phosphatase activity (119% of control,  $p < 0.05$ ), enlargement of centrilobular hepatocytes with fine eosinophilic granulation of the cytoplasm were observed in 320 ppm-treated males; all of these changes were reversible within the recovery period of 4 weeks; NOEL (M) = 80 ppm, (F) = 320 ppm (based adaptive responses of the liver to the test material); **acceptable**; (Leung, 10/5/92).

005; 114443; "Toxicity Test of HOE 33171 OH AT 203 in a 32-Day Study with SPF-Mice" (Leist et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 336/80, 6/10/80); HOE 33171 OH AT 203 (Batch # 2067, 97% purity); 0, 80, 315, 1250, and 5000 ppm in daily diet for 32 days; 10 mice/sex/dose; animals in the 5000 ppm-group had to be killed prematurely after 8-9 days because of poor general health condition, refusal of food and marked decrease in body weight; elevated SGPT and alkaline phosphatase, increased relative weights of the liver at dose levels higher than 315 ppm and isolated necrosis of the liver cells in mice that were killed prematurely indicates liver toxicity; eosinophilic, fine-granulated, partly markedly enlarged hepatocytes, extending in most cases all over the liver lobule were observed in the 315 ppm-dosage group, intensifying with increasing concentrations; these changes were also visible in the 80 ppm-group but less pronounced; tubular lesions in the kidneys were reported in females treated at 315 ppm and higher dosages; NOEL (M/F) < 80 ppm (based on changes in liver weight, enzyme activities, and histopathology); **supplemental**; (Leung, 10/6/92).

006; 114444; "Toxicity Test of HOE 33171 OH AT 204 in a 30-Day Study with SPF-Mice" (Leist et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 356/81, 3/10/81); HOE 33171 OH AT 204 (TGAI); 0, 5, 10, 20, and 80 ppm in daily diet for 30 days; 10 mice/sex/dose; behavior and general state of health of the animals in all test groups were normal throughout the study; no compound-related changes in body weight and food consumption; increased liver weights (115% and 119% of control, respectively,  $p < 0.05$ ) reported in females dosed with 20 and 80 ppm and in males of the 80 ppm group (125% of control,  $p < 0.05$ ); histopathological exam exhibits dose-dependent changes in the form of enlarged hepatic epithelia with relatively large nuclei and dense eosinophilic cytoplasm in the centrilobular regions of the liver; no indication of liver cell necrosis or changes in serum level of alkaline phosphatase was detected; NOEL (M) = 20 ppm, (F) = 10 ppm (based on liver weight and histopathological changes); **supplemental**; (Leung, 10/7/92).

007; 114445; "Repeated-dose (30 Days) Oral Toxicity Study of HOE 33171 OH AT 203 in Beagle Dogs" (Brunk et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 165/80, 3/3/80); HOE 33171 OH AT 203 (TGAI); 0, 80, 400 (29.4 and 24.3 mg/kg/day for males and females, respectively), and 2000 ppm in daily diet for 30 days; 2 beagle dogs/sex/dose; due to poor, moribund conditions, all dogs from the 2000 ppm group were killed prematurely; remaining dogs survived the study until scheduled termination; fatty degeneration of the liver and elevated alkaline phosphatase suggested liver

toxicity at the high dose; other observations included atrophy of the splenic capsule and thymus; one dog from the 400 ppm group showed siderosis of the lung, atrophy of the thymus and hyperplasia of the lymph follicles in the thyroid; NOEL (M/F) = 80 ppm (based on hepatotoxicity and other organ changes); **supplemental**; (Leung, 10/7/92).

008; 114446; "Repeated-Dose (3-Month) Oral toxicity Study of HOE 33171 OH AT 204 in Dogs" (Brunk et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 674/81, 11/24/81); 821; HOE 33171 OH AT 204 (96% purity); 0, 16, 80, and 400 ppm in daily diet for 3 months; 6 dogs/sex/dose; 2 dogs/sex/dose were maintained for an additional 4 weeks to monitor their recovery; all dogs survived the study up to scheduled termination; no treatment-related changes in clinical signs, body weight, food consumption, hematology, and clinical chemistry were reported; chronic interstitial pyelonephritis detected in mid (3/6 males) and high (3/6 males and 3/6 females) dose animals; a single case of chronic pyelonephritis was detected in a mid dose male during the recovery period; NOEL (M/F) = 16 ppm (based on chronic interstitial pyelonephritis); **unacceptable but possibly upgradeable** with submission of analyses of test diet to confirm the content of HOE 33171 OH AT 204 in the vehicle (corn meal); (Leung, 10/9/92).

#### Derma

009; 114447; "Subchronic (21-day) Repeated dose Dermal Toxicity Study with HOE 33171 - Substance Technical Grade in Rats" (Leist, Research & Consulting Co. AG, Itingen, Switzerland, Project # 28710, 10/2/84); 822; HOE 33171 OH ZD96 0001 (96.5% purity); 0 (sesame oil), 20, 100, and 500 mg/kg; applied on shaved skin site and covered with occlusive dressing for 6 hrs/day, 5 days/week for 21 applications; 6 rats/sex/dose; additional 5 rats/sex for the control, mid- and high-dose groups were maintained 4 weeks postdose to monitor their recovery; all rats survived until their scheduled termination; high dose males exhibited reduced body weight (91% of control,  $p < 0.05$ ) and food consumption during weeks 2 - 4 of treatment; dose related increases in relative liver weights (116.3 - 140.4% of control,  $p < 0.01$ ) without any abnormal histopathology observed in high and mid dose animals; similar increases in absolute and relative kidney weights (117.6% of control,  $p < 0.01$ ) were reported in high dose animals; NOEL (M/F) = 20 mg/kg (changes in relative liver and kidney weights); **acceptable**; (Leung, 10/14/92).

009; 114448; "Subacute (21-day) Repeated Dose Dermal Toxicity Study in Rats" (Ullmann et. al., Research & Consulting Company AG, Itingen, Switzerland, Project # 82642, 5/12/87); 822; HOE 33171 OH ZD98 0001 (96.5% purity); 0 (sesame oil), 5, 10, and 20 mg/kg; applied on shaved skin site and covered with occlusive dressing for 6 hrs/day, 5 days/week for 21 applications; 10 rats/sex/dose; two high dose females died on day 32 (one spontaneously and the other one after blood sampling); no treatment-related changes in body weights, food consumption, ophthalmology, biochemistry, urinalysis, organ weights, and necropsy were detected; no effects at HDT; histopathology not performed; NOEL not determined; **unacceptable and not upgradeable**; (Leung, 10/15/92).

010; 114541; "Subacute 21-day Repeated Dose Dermal toxicity with HOE 33171 in Rats: Confined Study Identification of target Organs by Organ Weight Measurement" (Ullmann, et. al., Research & Consulting Co. AG, Itingen, Switzerland, Project # 95455, 12/21/87); HOE 33171 OH ZD98 0001 (96.5%

purity); 0 (sesame oil), 5, and 20 mg/kg; applied on shaved skin site and covered with occlusive dressing for 6 hrs/day, 5 days/week for 21 applications; 10 rats/dose/sex; all animals survived the study until their scheduled termination; slight scales and maculate erythema were observed in three high dose females during weeks 1 and 2; no treatment-related changes in food consumption, body weights, ophthalmology, organ weights, and necropsy were detected; NOEL not determined; **supplemental**; (Leung, 10/16/92).

### Inhalation

011; 114450, 114451; "Subchronic (28 Exposures in 6 Weeks) Repeated Dose Inhalation Toxicity Study in Rats" (Leist, K. H., Research & Consulting Company AG, Itingen, Switzerland, Project #'s 28697 and 34233, 10/3/84); 824; HOE 33171 OH ZD96 0001 (96.5% purity); 0 (air), 0 (acetone), 0.014, 0.073, 0.248, and 0.727 mg/l (analytical); nose only exposure; 6 hrs/day, 5 days/week for a total of 28 exposures; >50% of the particles < 7  $\mu$ ; 6 rats/dose/sex for main study and 5 rats/sex from each group except for the low dose were used for a 4-week recovery period; one high-dose female died accidentally during exposure on day 1; dose-related increases ( $p < 0.05$ ) in absolute and relative liver and kidney weights at doses  $> 0.073$  mg/l; centrilobular hepatocellular hypertrophy in animals treated at 0.248 and 0.727 mg/l; elevated serum alkaline phosphatase in 0.073 and 0.248 mg/l-treated males rats and in high dose animals; after the 4-week recovery period, no treatment-related changes in serum levels of alkaline phosphatase or centrilobular hepatocellular hypertrophy was observed; NOEL (M/F) = 0.014 mg/l (based on organ weight changes, serum chemistry, and histopathology); **acceptable**; (Leung, 10/21/92).

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## METABOLISM STUDIES

### Metabolism, Rat

031; 114500; "Metabolism in Male and Female Rats after Single and Repeated Oral Administration, Respectively, of a Low and a High Dose, Respectively" (Dorn et. al., Hoechst AG, Frankfurt, Germany, Report # Fo.336/84, 2/11/85); nonlabeled HOE 33171 OH ZB99 0001 (97% purity), Chlorophenyl-[U- $^{14}$ C]-fenoxa-prop ethyl (22.85 mCi/g, 98% radiochemical purity); oral; single: 2 and 10 mg/kg (10 - 15 rats/sex/dose), multiple: 14 daily nonlabeled doses followed by a radiolabeled dose on day 15 at 2 mg/kg (15 rats/sex); females excreted larger fractions of the radioactive dose in the urine as compared to males (65% vs. 49%, respectively,  $p < 0.05$ ) with the corresponding 30% to 44% of the radioactivity found in feces at all dose levels; no relevant qualitative differences in the metabolite pattern observed in any of the dose group; at the single low dose, there were no differences between males and females with the exception of a slightly higher percentage of free acid in urine of females (4.7%) than males (1.1%); however, repeated dosing at 2 mg/kg or at an increased dose level showed that females do not have additional capacity to metabolize all the absorbed material further beyond the free acid; in contrast, male rats absorbed the high dose to a lower extent but have the additional capacity to metabolize the absorbed material to products beyond the free acid; **supplemental**; (Leung, 11/12/92).

031; 114501; "HOE 33171 - dioxyphenyl-1-<sup>14</sup>C, Metabolism in Rats Orally Administered at Two Doses, 2 and 10 mg/kg Body Weight" (Burkle et. al., Hoechst AG, Frankfurt, Germany, Report # B 3/85, 1/3/85); dioxyphenyl-1-<sup>14</sup>C-fenoxaprop ethyl (11.36 mCi/g, 96% radiochemical purity); oral; single; 2 mg/kg (15 female rats), 10 mg/kg (10 rats/sex); urine and feces collected at 0-24 hours after treatment; females excreted a larger fraction of the total dose in urine as compared to males; male rats excreted only one main metabolite in urine: 2-(4-hydroxyphenoxy)- propionic acid (HPP-acid) which amounted to 47.5% of the dosage; however, female rats excreted both, HPP-acid and the free acid (HOE 53022) in ratios of 1:1 (54.5% of total dose) for the high dose and 2:1 for the low dose (71% of total dose); metabolic pattern in feces was independent of sex and unchanged parent compound (HOE 33171) and free acid were found in the same ratio; however, the ratio between HOE 33171 and HOE 53022 in feces from females were altered by dose level, 1:1 (10 mg/kg) and 1:3 (2 mg/kg); **supplemental**; (Leung, 11/13/92).

031; 114499; "Chlorophenyl-[U-<sup>14</sup>C]-Fenoxaprop-ethyl, on the Metabolism of the Herbicide in Rats" (Dorn, et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # F0.318/82, 12/16/82); Chlorophenyl-[U-<sup>14</sup>C]-Fenoxaprop-ethyl (Batch # 9024 IIg, S.A. = 2.635 mCi/g, 98% radiochemical purity) dissolved in salad oil; 40 mg/kg body weight administered to female SPF-Wistar rats by intragastric intubation; 50% of radioactivity in urine samples was identified as a mercapturic acid of 6-chlorobenzoxazol formed by cleavage of the ether bond between the heterocycle and the phenyl ring followed by conjugation of 6-chloro-benzoxazol to the sulfhydryl group of glutathione with subsequent cleavage of the glycine and glutamic acid moieties; three other urine metabolites each representing less than 5% of the total radioactivity in urine were also identified; remaining 36% radioactivity represent some water-soluble metabolite (s) which were not identifiable; two metabolites in feces were extracted from neutral and acidified water, whose original form could not be identified; however, both metabolites were shown to be 6-chlorobenzoxazol weakly bound to unknown structures; **supplemental**; (Leung, 11/9/92).

031; 114502; "Study of Kinetics and Residue Concentrations following Oral Application of 10 mg/kg Body Weight in Rats" (Kellner and Eckert, Hoechst AG, Frankfurt, Germany, Report # 01-L42-0439-84E, 11/30/84); Chlorophenyl-[U-<sup>14</sup>C]-Fenoxaprop-ethyl mixed with nonlabeled HOE 33171 OH ZB99 0001 and administered orally in sesame oil (12.02 mCi/g, 98% radiochemical purity) at 10 mg/kg to 5 SPF Wistar rats/sex; females eliminated 60.4% of the total dose or radioactivity via urine which is 27% more than that for males (43.9%); the amount of radioactivity excreted in the feces was reported to be 49% for males and 35% for females; the absorption half-life (t<sub>1/2α</sub>) was reported to be between 8 and 10 hr regardless of sex; the elimination half-lives (t<sub>1/2β</sub>) for urine and feces were reported to be 35.6 hr and 45 hr for males, and 69.4 hr and 26.5 hr for females, respectively; highest concentrations of residues were found in fatty tissues and kidneys; 98% - 100% of the administered dose or radioactivity was recovered at the completion of this study; **supplemental**; (Leung, 11/16/92).

031; 114503; "Study of Kinetics and Residue Determinations Following Oral and Intravenous Applications in Rats" (Kellner and Eckert, Hoechst AG, Frankfurt, Germany, Report # 01-L42-0364-82, 4/22/82); Chlorophenyl-[U-<sup>14</sup>C]-fenoxaprop-ethyl (Batch # 9024 II, 26.34 mCi/g, >98% radiochemical purity); 2.06 - 2.52 mg/kg administered intravenously or orally to 5 SPF Wistar rats/sex; the amount of radioactivity in expired air was minor and did not

exceed the limit of detection; maximum blood concentrations (C<sub>max</sub>) of 6.72 ug-equiv/ml in males and 4.53 ug-equiv/ml in females were reported at 6 to 8 hr (T<sub>max</sub>) after oral dosing; elimination was biphasic with t<sub>1/2α</sub> ranging from 6.4 to 14.6 hr and t<sub>1/2β</sub> was estimated to be 74.2 hr for both sexes; AUC (168 hr)s were determined to be 158.1 and 151.0 ug-equiv x hr/ml for males and females, respectively; the highest blood concentrations measured 5 minutes after intravenous administration were 4.22 and 5.12 ug-equiv/ml for males and females, respectively; elimination from blood following IV administration was characterized by three phases with three separate half-lives (t<sub>1/2α</sub>, t<sub>1/2β</sub>, and t<sub>1/2γ</sub>); 1.3, 11.2, and 97.5 hr in males and 0.72, 7.8, and 72.8 hr in females, respectively; no sex-dependent differences in AUC (168 hr)s were evident and a mean of 115.8 ug-equiv x hr/ml were reported for both sexes; comparison of area under the blood concentration-time curves between oral and intravenous administration was greater than 100% due to intersubject variability and suggests that absorption following oral dosing is virtually complete; **supplemental**; (Leung, 11/16/92).

031; 114504; "Study of Kinetics and Residue Concentrations Following Repeated Oral Applications of 2 mg/kg/day in Rats" (Kellner and Eckert, Hoechst AG, Frankfurt, Germany, Report # 01-L42-442-84E, 12/4/84); 14 daily oral doses of 2 mg nonlabeled HOE 33171/kg/day followed by a single oral dose of 2 mg [chlorophenyl-U-<sup>14</sup>C]-fenoxaprop ethyl (HOE 33171 OH ZE 98 0007, 22.85 mCi/g, 98% purity)/kg on day 15; 5 SPF Wistar rats/sex; renal excretion in female rats was 25% higher than in males; elimination of radioactive HOE 33171 and/or metabolites was biphasic and its rates are comparable to animals receiving a single dose; absorption half-life (t<sub>1/2α</sub>) was reported to be between 8.5 to 12.5 hr for urine and feces regardless of sex; the elimination half-life (t<sub>1/2β</sub>) with urine was 41.3 hr for females and 72.5 hr for males; with feces t<sub>1/2β</sub> was estimated to be 27.3 hr for males and 33.7 hr for females; highest concentrations of residues were located in kidneys, fatty tissues, and blood; no evidence for accumulation of the test material and/or its metabolites following multiple dosing; **supplemental**; (Leung, 11/17/92).

031; 114505; "Comparative Investigation of the Metabolism and Radioactivity Levels of Tissues in the Pregnant Cynomolgus Monkey, Rabbit, and Rat After Oral Administration of the Active Ingredient via Stomach Tube" (Dorn et. al., Hoechst AG, Frankfurt, Germany, Report # Fo.330/84, 10/1/84); multiple daily oral administration of nonlabeled HOE 33171 (technical grade) to pregnant cynomolgus monkey (10 mg/kg), rabbits (50 mg/kg) and rats (50 mg/kg) during embryo organogenesis; the first dose for the monkey and the final dose for all the animals was radiolabeled HOE 33171 (technical grade); no direct comparison in the blood level of radioactivity with the monkey is possible since the administered dose is 5 times lower than that given to rabbits and rats; however, a dose correction of 5 folds, suggested that blood levels of radioactivity in monkey is the lowest of three species; highest level of residues are localized in the kidney, liver and blood; except for the kidneys, all other organs and tissues showed a 2 to 4 fold higher concentrations of radioactive residues in rats than rabbits at 6 and 48 hours after the final dose; radioactivity level was higher in rat fetuses than rabbit fetuses (10.0 vs. 1.5, respectively, at 6 hours after the final dose); higher concentrations of free acid (HOE 53022) in rat livers than in rabbit livers support the contention that the metabolizing capacity of rats is lower than that of rabbits; mercapturic acid of 6-chlorobenzoxazol was detected in all three species; after dose correction, this metabolite was three times less than in rabbits and rats which is consistent with the finding that primates

have a lower level of glutathione transferase when compared to rats and rabbits; **supplemental**; (Leung, 11/18/92).

Summary: Following oral administration, 94% of the radiolabeled fenoxypop ethyl is eliminated primarily via urine and feces by 168 hours. Female rats excreted a larger fraction or 25% more of the radioactive dose in the urine as compared to male rats. The amount of radioactivity found in expired air was minor and did not exceed the limit of detection. Multiple dosing and higher dose level did not alter the route of excretion or result in the retention of the test substance. Metabolism of fenoxaprop ethyl leads first to the free acid and then to 2-(4-hydroxyphenoxy)-propionic acid (Hp-acid) and mercapturic acid of 6-chloro-benzoxazol formed by cleavage of the ether bond between the heterocycle and the phenyl ring followed by conjugation to glutathione. At single low doses there were no quantitative differences in metabolic profile between male and female rats. However, multiple dosing or increased dose levels demonstrated that female rats do not have additional capacity to metabolize all of the absorbed test material and consequently excrete a higher amount of the free acid in the urine. In contrast, male rats absorbed the high dose to a lower extent but have the additional capacity to metabolize the absorbed test material to products beyond the free acid. (Leung, 12/22/92)

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SPECIAL TOXICOLOGICAL STUDIES

021; 114507; "Hepatotoxicity Screening by Histological and Biochemical Methods in Rats" (Ebert et. al., Hoechst AG, Frankfurt, Germany, Report # 215/82, 7/28/82); HOE 33171 OH AT 204 (Serial # 9707, Op. 3/80, technical) 0 (diet), 2, and 20 mg/kg administered daily in diet to 15 rats/sex/dose for 30 successive days; 5 rats/sex/dose were killed at the end of the treatment period, and after 14 and 28 day recovery period; behavior, general health condition, bodyweight gains, food and water consumption were not affected by the test material; no treatment-related changes in relative and absolute liver weights; administration of the test material did not produce any signs of peroxisomal proliferation, depletion of glutathione, or induction of foreign substance metabolizing enzymes; **supplemental data** (Leung, 12/14/92).

022; 114508; "Hepatotoxicity Screening by Histological and Biochemical Methods in Mice" (Ebert et. al., Hoechst AG, Frankfurt, Germany, Report # 537/82, 9/8/82); HOE 33171 OH AT 204 (Serial # 9707, Op. 3/80, technical); 0 (diet), 2, and 20 mg/kg administered daily in diet to 15 rats/sex/dose for 30 successive days; 5 rats/sex/dose were killed at the end of the treatment period, and after 14 and 28 day recovery period; daily administration of the test material in the diet had no effect on the behavior or general health condition of all the animals; at the end of the treatment period, enzyme biochemistry workup indicated lowering of glutathione in both sexes by 80 - 85% of control ( $p < 0.05$ ) and an elevated catalase activity to about 150% of control in males ( $p < 0.05$ ); these changes were not considered to be toxicologically significant since there were no macroscopic or microscopic signs of hepatotoxicity and by the 28th day of the recovery period these changes in enzymatic activities were reversible; **supplemental data** (Leung, 12/15/92).

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SB950-MANDATED HEALTH EFFECTS STUDIES

Chronic Toxicity, Rat

\*\* 014, 015; 114454, 114455; "Chronic Feeding Study (24 months) in Rats", (Kramer, et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 9/19/84); 831; HOE 33171 OH AT 206 or HOE 33171 OH AS 201 (both are TGAI); 0 (diet), 5, 30, and 180 ppm (males: 0, 0.26, 1.58, and 9.43 mg/kg, respectively; females: 0, 0.33, 2.00, and 11.87 mg/kg, respectively); 20 rats/sex/dose; 6 rats/sex/dose for BSP/PSP function test and another 10 rats/sex/dose used for monitoring residues in organs and tissues; mortalities: males 1/20, 7/20, 2/20, 3/20; females 7/20, 7/20, 7/20, 6/20, respectively; **no adverse effect**; no treatment-related changes in body weight, food consumption, hematological parameters, urinalysis, and clinical chemistry were detected; levels of residues found in organs and tissues from the treated animals were dose-related but there was no sex differences or time-related accumulation of residues; reduction in absolute (88.7% of control,  $p \leq 0.05$ ) and relative (89.8% of control,  $p \leq 0.05$ ) liver weight in high dose males was not considered to be toxicologically significant in the absence of any abnormal histological changes; hepatic (BSP) and renal (PSP) tests did not reveal any functional disturbances due to HOE 33171; NOEL (M/F) = 30 ppm (males: 1.58 mg/kg, females: 2.00 mg/kg, based on induction of hepatic enzymes, changes in liver weights, distension of the zona reticularis and the medulla of the adrenals, hyperplastic epithelia of the renal pelvis with calcareous deposits); **acceptable**; (Leung, 10/30/92).

012; 114452; "Chronic Feeding Study in Rats (Interim Killing after 6 months)" (Kramer et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 1/10/83); HOE 33171 OH AS 201 or HOE 33171 OH AT 206 (both are TGAI); 0(diet), 5, 30, and 180 ppm; 10 rats/sex/dose; one low dose male rat died during week 3 due to hemorrhage of the urinary bladder; all other animals survived until scheduled termination; **no adverse effects indicated**; high dose males exhibited increased body weight (110% of control,  $p < 0.05$ ) without any changes in food consumption; rats from the 180 ppm group showed partially hyperplastic epithelia of the renal pelvis with calcareous deposits (10/20 vs. 6/20 in 180 ppm and control group, respectively); **supplemental**; (Leung, 10/22/92).

013; 114453; "Chronic Feeding Study in Rats (Interim Killing After 12 Months)" (Kramer et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 11/11/83); HOE 33171 OH AS 201 or HOE 33171 OH AT 206 (Both are TGAI); 0 (diet), 5, 30, and 180 ppm; 10 rats/sex/dose; all animals survived the study until scheduled termination; **no adverse effects indicated**; no treatment-related changes in behavior, clinical signs, body weight, food consumption, hematological parameters, and urinalysis were detected; elevated aminopyrine N-demethylase activity (223.5% of control,  $p < 0.05$ ) in high dose females and carnitine acetyltransferase activity (403.1 - 537.9% of control,  $p < 0.05$ ) in high dose animals; histological exam revealed distension of the zona reticularis and medulla of the adrenals in high dose animals in the absence of discernible tissue lesions; **supplemental**; (Leung, 10/26/92).

Chronic Toxicity, Dog

\*\* 018, 065; 114458, 121144; "Toxicological Testing of HOE 33171 by Repeated Oral Administration to Beagle Dogs for 2 Years" Brunk et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 85.0073,

1/30/85); 831; HOE 33171 OH ZC94 0001 (94% purity); 0 (cornmeal), 3, 15, and 75 ppm (males: 0, 0.20, 1.10, and 5.2 mg/kg, respectively; females: 0, 0.18, 0.90, and 4.60 mg/kg, respectively) to 6 dogs/sex/dose for 2 years; all animals survived the study until scheduled termination; no adverse effects; high dose females and males demonstrated reduced body weight gain (49.1 and 54.6% of control,  $p < 0.05$ , respectively) without any abnormal changes in food consumption; no treatment-related changes in clinical signs, ophthalmological findings, hematological parameters, clinical chemistry, and urinalysis were detected; hepatic (BSP) and renal (PSP) function tests did not reveal any organ dysfunction; NOEL (M/F) = 15 ppm (males: 1.1 mg/kg, females: 0.9 mg/kg, reduced body weight gain); study originally reviewed as unacceptable but possibly upgradeable with analysis of test diet to confirm the actual concentrations of HOE 33171 employed; (Leung, 11/4/92); study was rereviewed with test diet analysis; **acceptable**; (upgraded, Leung, 3/4/93).

\*\* 017, 065; 114506, 121146; "Toxicological Testing of HOE 33171 by Repeated Oral Administration to Beagle Dogs for One Year" Brunk et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 84.0437, 7/19/84); 831; HOE 33171 OH ZC94 0001 (94% purity); 0 (cornmeal), 3, 15, and 75 ppm to 6 dogs/sex/dose for 1 year; 1 mid dose male was killed on day 106 due to poor health conditions produced by intestinal stenosis following fatty tissue necrosis; all remaining animals survived the study until scheduled termination; **no adverse effects**: no treatment-related changes in body and organ weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, necropsy and histology; normal hepatic and renal functions; NOEL (M/F)  $\geq$  75 ppm (no effect at HDT); study originally reviewed as unacceptable but possibly upgradeable with analysis of test diet to confirm the actual concentrations of HOE 33171 employed; (Leung, 11/3/92) study was subsequently reviewed with test diet analyses; **acceptable**; (upgraded, Leung, 3/4/93).

#### Combined, Rat

\*\* 015, 016; 114456, 114457; "Combined Chronic Toxicity and Carcinogenicity Study in Rats (24 and 28 month feeding studies)", Kramer et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 6/28/85); this study represents another segment of a 24 month chronic feeding study in rats (document 51910-014, -015, record #s 114454 and 114455); 835; HOE 33171 OH AT 206 or HOE 33171 OH AS 201 (both are TGAI); 0 (diet), 5, 30, and 180 ppm to 60 rats/sex/dose for 28 months; **no adverse effects**: no treatment-related changes in mortality, body weight, food consumption, hematological parameters, and urinalysis detected; lowering of serum cholesterol (78.3% of control,  $p < 0.05$ ) and total lipids (75.8% of control,  $p < 0.05$ ) reported in high dose males; induction of hepatic enzymes in high dose animals at 12 months with reduced relative liver weight in mid- and high-dose males (88.7% of control,  $p < 0.05$ ); was not considered to be toxicologically significant without any abnormal findings in histology or hepatic function test at 24 months; distension of zona reticularis and the medulla of the adrenals and hyperplastic epithelia of the renal pelvis with calcareous deposits at 24 months was also detected; age-related dystrophy of sciatic nerve and femoral muscle in control and treated animals; no oncogenic potential demonstrated with chronic feeding; NOEL (M/F) = 30 ppm (based on serum levels of cholesterol and total lipids, induction of hepatic enzymes, histological changes in the adrenals and kidneys; **acceptable**; (Leung, 11/5/92).

### Oncogenicity, Mouse

\*\* 020; 114461; "HOE 33171 - Carcinogenicity Study in Mice (24-month Feeding Study)", Kramer et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 695, 3/11/85); HOE 33171 OH AS 201 (TGAI, 94% purity); 0 (diet), 2.5, 10, and 40 ppm to 50 mice/sex/dose for 24 months; mortalities were reported in all groups during the last 6 months of the study: males 14/50, 21/50, 21/50, 19/50; females 21/50, 30/50, 26/50, 20/50, respectively; no treatment-related changes in body weight, food consumption, hematological parameters, and clinical chemistry; reduced absolute and relative liver weights (85% of control,  $p < 0.05$ ) in mid and high dose females without any abnormal histological findings; **no adverse effect**; NOEL (F) = 40 ppm, (M) = 40 ppm (no effect at HDT); **acceptable**; (Leung, 11/6/92).

019; 114459, 114460; "HOE 33171 - Chronic Feeding Study in Mice (Interim Killing after 12 Months)", Kramer et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 695, 11/25/83); HOE 33171 OH AS 201 (TGAI, 94% purity); 0 (diet), 2.5, 10, and 40 ppm to 10 mice/sex/dose for 12 months; **no adverse effects indicated**; all animals survived the study until scheduled termination; no treatment-related changes in clinical signs, body weight, food consumption, hematological parameters, serum biochemistry, macroscopic and histological examinations were detected; dose-related increase in absolute and relative kidney weights in high dose animals was not considered to be toxicologically significant because there was no histological correlation; this increase in kidney weight was only statistically significant in high dose females (108.4% of control,  $p < 0.05$ ); HOE 33171 did not induce biosynthesis of hepatic enzymes of foreign substance metabolism or cause peroxisomal proliferation; NOEL (M)  $\geq$  40 ppm (no effect at HDT), (F) = 10 ppm (kidney weight changes were only seen at 12 month interim killing but not at terminal killing at 24 months); **supplemental**; (Leung, 11/5/92).

### Reproduction, Rat

027; 114478; HOE 33171-Technical Grade: Effects of Dietary Administration upon Reproductive Function in the Rat 1. Dosage Range-Finding Study, J.M. Tesh et al.; Rat; 834; Life Science Research, Essex, England; LSR Report No. 83/HAG085/376; 2/14/85; HOE 33171 Technical Grade (Code: HOE 33171 OH AS 201), purity: 94.0%; F(0) 6 animals/sex/group; F(1) not mated; Dose (dietary): 0, 40, 160, 320 ppm; Mortality: No deaths for F(0), F(1)-0 (4/69), 40 (0/57), 160 (2/62), 320 (3/45) by day 21 post partum; Observations: no treatment-related signs, no treatment-related effect on body weight gain or food consumption; Necropsy: no treatment-related lesions reported, significant increase in relative liver weight (F(0) males, 320 ppm), in absolute liver weight (F(1) males, 40, 160, 320 ppm), in absolute kidney weight (F(1) males 40, 160, 320 ppm), decrease in absolute thymus weight (F(1) female, 320 ppm); Reproductive factors: no. of implantations, litter size reduced in 320 ppm group, no effect upon mating, fertility index, gestation index; Development: no treatment-effect upon viability index, lactation index, and mean pup weight; Study **supplemental**. (Moore, 11/5/92)

\*\* 028; 114479; HOE 33171-Technical Grade: Effects upon Reproductive Performance of Rats Treated Continuously Throughout Two Successive Generations, J.M. Tesh et al.; Rat; 834; Life Science Research, Suffolk, England; LSR Report No. 84/HAG087/636, purity: 94.0%; 5/13/85; HOE 33171 Technical Grade (Code: HOE 33171 OH AS 201); 30 animals/sex/group both F0, F1; 2 generations, 2 matings/generation; Dose (dietary): 0, 5, 30, 180 ppm; Mortality: (adults) deaths not treatment-related; Observations: no treatment-related signs or treatment-related effects upon body weight gain or food consumption, both generations; no treatment-related effect upon estrus cycles, pre-coital interval, mating performance, conception rate, gestation length, gestation indices (all matings); no treatment-related effects on live births, viability, sex ratios, development parameters (all matings); Necropsy: no macroscopic lesions adult or offspring; (adults) increased absolute and relative liver weight (M/F:180 ppm), (offspring) increased absolute and relative liver weight (M/F:180 ppm), increased relative kidney weight (M/F:180 ppm), increased absolute and relative thymus weight (M/F:180 ppm); Histopathology: Kidney, increased incidence of nephrocalcinosis in offspring and adult females; Possible target organ: kidney; **No adverse effects**; Adult NOEL:30 ppm (based on increased liver weight, nephrocalcinosis, 180 ppm); Reproductive NOEL:180 ppm; Developmental NOEL:30 ppm (based on increased kidney and liver, and reduced thymus weight, nephrocalcinosis, 180 ppm); Study **acceptable**. (Moore, 11/18/92).

029; 114481; Multiple Generation Study on HOE 33171 Substance Technical Grade in Rats, H. Becker et al; 834; Rat; RCC Research and Consulting Company, Itingen, Switzerland; Project No. 034896; 2/20/86; HOE 33171 Technical Grade (Code: HOE 033171 OH ZD97 0001), purity: 97.2%; 30 animals/sex/group, both F0, F1; 2 generations, 2 matings/generation; Dose (dietary): 0, 5, 30, 180 ppm; Mortality: (adults) deaths not treatment related; Observations: (adults) no treatment-related signs or treatment-related effects upon body weight gain or food consumption for both generations; absolute and relative liver and kidney weight increase (M/F:180 ppm); (offspring) mean body weight reduced (180 ppm) 21 days post partum, all matings, increased absolute and relative liver and kidney weights (M/F: 180 ppm); decreased absolute and relative thymus (M/F:180 ppm) and spleen weights (F:180 ppm); Clinical Chemistry: (adults) total lipids reduced (F1, 180 ppm), (offspring) alkaline phosphatase increased (all matings, 180 ppm); Reproductive, Developmental: no treatment-related effect upon estrus cycles, precoital interval, mating performance, conception rate, gestation length, gestation indices, all matings; no treatment-related effects upon live births, viability, sex ratio, developmental parameters for offspring, all matings; Necropsy: no data submitted; Histopathology: no data submitted; NOEL (preliminary): adults-30 ppm (based on significant increase in liver and kidney weights, decrease in thymus weights in 180 ppm group), reproductive: 180 ppm, developmental-30 ppm (based on reduced body weights at 21 days in 180 ppm group); Study **unacceptable, may be upgraded** with submission of necropsy and histopathology data. (Moore, 11/17/92).

#### Teratology, Rat

\*\* 023, 065; 114464, 114465, 121148; "An Oral Embryotoxicity Study of Hoe 33171 O H AT 204 in Wistar Rats" (authors: Drs. Baeder, Weigand, & Kramer); 833; Pharma Research Toxicology, Hoechst, Frankfurt, Germany; report #613/82; 10/4/82; Hoe 33171 O H AT204 (fenoxaprop ethyl); 93.0% purity; administered daily by gavage between gestation days 7-16; doses: 0 (sesame

oil), 10, 32, & 100 mg/kg/day; dams sacrificed on day 21; 20 dams/dose; no maternal deaths; slight decrease in maternal food consumption and weight gain compared to controls and appearance of piloerection in several dams at the high dose; 0/60 dams at 0, 10, & 32 mg/kg/day suffered early abortion or fetal death while 4/40 did so at 100 mg/kg/day; high-dose fetuses weighed slightly less than controls ( $2.97 \pm .20$  g vs.  $3.34 \pm .37$  g,  $p < .001$ ), were slightly shorter ( $3.52 \pm .11$  cm vs.  $3.61 \pm .12$  cm,  $p < .025$ ), displayed weak ossification at 3 sites and anlage of a 14th rib at the 1st lumbar vertebra, and had slight tendencies toward thickened, bent, undulating ribs and fragmented, dysplastic, dislocated, longitudinally displaced, fused sternbrae; reported maternal NOEL=32 mg/kg/day; reported developmental NOEL=32 mg/kg/day; study originally reviewed as unacceptable but possibly upgradeable upon submission of analyses of the dosing solutions; (Rubin, 11/17/92); subsequently rereviewed with dosing solution analyses; **acceptable**; (upgraded, Leung, 3/5/93).

51910-024; 114466; "A Study of the Effect of the Active Ingredient Hoe 033171-Technical on Pregnancy of the Rat" (authors: P. James, R. Billington, R. Clark, & J. Offer); 833; Huntingdon Research Centre, Cambridgeshire, England; report #223/83691; 12/12/83; Hoe 33171 O H ZC96 0002 (fenoxaprop ethyl); 96.2% purity; administered daily by gavage between gestation days 6-15; doses: 0 (sesame oil), 10, 32, & 100 mg/kg/day; 25 dams/dose (24 were pregnant), sacrificed on day 20; no maternal deaths; maternal effects: increased water consumption at 32 & 100 mg/kg/day between days 9-11, decreased weight gain at 100 mg/kg/day between days 6-10, increased liver weight upon sacrifice at 100 mg/kg/day; fetal effects: decreased mean fetal weight at 100 mg/kg/day, increased mean % malformations at 100 mg/kg/day (though not statistically significant), increased mean % visceral anomalies at 32 and 100 mg/kg/day, increased mean % skeletal anomalies at 100 mg/kg/day, increased mean % unossified sternbrae (a type of "variation") at 100 mg/kg/day, and decreased mean % normal sternbrae at 100 mg/kg/day; maternal NOEL=100 mg/kg/day, developmental NOEL=10 mg/kg/day; **Unacceptable** (but possibly upgradeable upon submission of analyses of dosing solutions). (Rubin, 11/19/92)

024; 114467; "Embryotoxicity Study in the Rat (Dermal Application)" (Leist, K. H., Research & Consulting Company AG, Itingen, Switzerland, Project # 28765, 10/17/84); 833; HOE 33171 OH ZD96 0001 (96.5% purity); nominal doses of 0 (sesame oil), 100, 300 and 1000 mg/kg/day administered dermally to 25 pregnant female rats/dose for 6 hours/day from days 6 through 15 of gestation; **no adverse effects indicated**; no mortalities were reported; local effects at the application sites consisted of very slight erythema in two to four dams in each of the four dose groups for two to three days; no test article-related differences in the mean number of implantations, resorptions and fetal weight or evidence of embryonic and/or teratogenic potential was detected; nominal maternal and developmental NOEL  $\geq$  1000 mg/kg/day ("limit" test); **unacceptable but possibly upgradeable** with submission of dosing solution analysis to confirm the actual amount of the test article applied dermally; (Leung, 12/11/92).

024; 114468; "Testing for Embryotoxicity and Effects on Postnatal Development in Wistar Rats Following Oral Administration" (Baeder et. al., Hoechst AG, Frankfurt, Germany, Report # 86.0133, 2/4/86); 833; HOE 33171 OH ZD98 0001 (97.9% purity); nominal doses of 0 (sesame oil), 10, 32, and 100 mg/kg administered orally daily to 20 - 22 pregnant/dose on days 7 to 16 of pregnancy; all females allowed to deliver and rear their offsprings for 21-23 days; one low dose animal died during the night after the 8th treatment due to faulty intubation and was replaced; slight reduction in maternal body weight (95.1% of control,  $p < 0.05$ ) accompanied by reduced food consumption (85.5% of control,  $p < 0.05$ ) at 100 mg/kg was reversible by the end of the study; clinical findings included local alopecia and scabbing and piloerection in all three treated groups; **no adverse effects indicated**; no difference between the numbers of live offsprings per litter in the three treated groups as compared with the control group; offsprings in the treated groups were normally developed and their body weights at birth were comparable with those of the control animals; viability of the offsprings in all three dose groups was unimpaired; nominal maternal and developmental NOEL  $\geq 100$  mg/kg/day (no effect at HDT); **unacceptable but possibly upgradeable** with submission of analysis of dosing solutions to confirm the actual dosage administered; (Leung, 12/14/92).

#### Teratology, Rabbit

\*\* 025, 065; 114469, 114470, 121148; "An Oral Embryotoxicity Study of HOE 33171 Active Ingredient (Technical Grade) (Code: HOE 33171 OH AT204) in Himalayan Rabbits" (Baeder et. al., Hoechst AG, Frankfurt, Germany, Report #'s 667/82 and 86.0022, 10/21/82); HOE 33171 OH AT 204 (Batch 10750, 93% purity); 833; nominal doses of 0, 12.5, 50, and 200 mg/kg/day in sesame oil to 15 pregnant Himalayan rabbits/dose on the 7th - 19th day of pregnancy; 1 and 2 dams from the low and high dose groups, respectively, were reported dead between the 16th and 19th day of pregnancy; administration of 200 mg/kg to dams led to a decrease in food consumption with a reduction in body weight and increased incidence of abortions; however, on the 20th day of pregnancy when treatment with HOE 33171 was terminated, surviving dams consumed normal quantity of feed with concomitant body weight gain and partial recovery of body weight; fetuses at the high dose exhibited growth retardation, reduced survival rate, diaphragmatic hernias and increased incidence of a 13th rib; **no adverse effects**; maternal and developmental NOEL  $> 50$  mg/kg/day (growth retardation, reduced survival rate, increased incidences of abortions and 13th rib); originally reviewed as unacceptable and not upgradeable; lack of dosing solution analyses to confirm the actual dosage administered and all fetuses were not subjected to both visceral and skeletal examinations; (Leung, 11/19/92); subsequently reviewed with dosing solution analyses and additional data from another rabbit teratology study (record #'s 114471 and 114472); **acceptable**; (upgraded, Leung, 3/5/93).

\*\* 025, 065; 114471, 114472, 121148; "Testing for Embryotoxicity in Himalayan rabbits Following Oral Administration" (Baeder et. al., Hoechst AG, Frankfurt, Germany, Report #'s 83.0516 and 86.0019, 9/29/83); 833; HOE 33171 OH ZC 96 0002 (Serial # 11977, 96.2% purity); 833; nominal doses of 0, 2, 10, and 50 mg/kg/day in sesame oil to 15 pregnant Himalayan rabbits/dose on the 7th - 19th day of pregnancy; Except for one high-dose dam which had died because of vaginal bleeding, all other remaining dams survived the study until scheduled termination; high dose dams exhibited slightly lower food consumption during days 7 - 14, but subsequently returned to normal; delivered fetuses in all dose groups were normally developed and showed no impairment of viability

during the first 24 hours; **no adverse effects**; maternal and developmental NOEL > 50 mg/kg/day (no effect at HDT); originally reviewed as unacceptable and not upgradeable; lack of dose solution analyses to confirm the actual dosage administered and all fetuses were not subjected to both visceral and skeletal examinations; (Leung, 11/30/92); subsequently reviewed with dosing solution analyses and additional data from another rabbit teratology study (record #s 114469 and 114470); **acceptable**; (upgraded, Leung, 3/5/93).

Summary: Considering both rabbit teratology studies together, the number of fetuses examined for visceral and skeletal abnormalities is adequate.

026; 114473; "Embryotoxicity Study in the Rabbit (Dermal Application)" (Leist, K. H., et. al., Research & Consulting Company AG, Lofingen, Switzerland, Project # 28776, 10/3/84); 833; HOE 33171 OH 1096 0001 (96.5% purity); nominal doses of 0 (sesame oil), 100, 300, and 1000 mg/kg administered dermally 6 hours/day to 16 dams/dose from days 6 through 18 of pregnancy; no mortalities or abnormal clinical findings were reported during this study; erythema, edema, desquamation, exfoliation, and fissuring occurred in all animals and no dose-related differences in intensity of the skin irritations were observed; one dam in the low dose group had only 4 implantation sites and another in the mid dose group had 9 embryonic resorptions on day 28; live fetuses were not found in either dams; no treatment-related differences in reproductive parameters were noted and there was no evidence of embryonic and/or teratogenic potential of the applied test article; **no adverse effects indicated**; nominal maternal and developmental NOEL > 1000 mg/kg/day (no effect at HDT); **unacceptable but possibly upgradeable** with submission of dose solution analyses to confirm the actual amounts of test article applied dermally; (Leung, 12/4/92).

#### Teratology, Mouse

026; 114474; "Study of the Effect of the Active Ingredient HOE 33171-Technical on Pregnancy of the Mouse" (James, P. et. al., Huntingdon Research Center PLC., Cambridgeshire, UK, Report # HST 221/222-R 83666, 11/14/83, Re-issued with amended pages on 1/10/85 ); 833; HOE 33171 OH 1096 0002 (TGAI); 0 (sesame oil), 2, 10, and 50 mg/kg/day administered orally to 30 dams/dose from days 6 through 15 of pregnancy; no mortalities or treatment-related body weight changes were reported; high dose dams exhibited increased absolute liver weight (125.65% of control, P<0.01) with occasional discoloration of the liver; no treatment-related differences in reproductive parameters were noted and there was no evidence of teratogenic potential of the administered test material; **no adverse effects indicated**; nominal maternal and developmental NOEL > 50 mg/kg/day (no effect at HDT); study **unacceptable but possibly upgradeable** with submission of dosing solution analysis and dose level justification; (Leung, 12/8/92).

#### Teratology, Monkey

027, 065; 114475, 121151; "Oral Embryotoxicity Study in the Cynomolgus Monkey" (Osterburg, Hazleton Laboratories Deutscher and GmbH, Munster, FRG, Project # 169/6, 11/12/84); 833; HOE 33171 OH 1096 0002 (96.2% purity); 10 and 50 mg/kg/day administered orally to 23 and 11 pregnant Cynomolgus monkeys, respectively, from days 20 through 50 of gestation; **no adverse effects indicated**; 5/21 pregnant animals in the low dose group aborted their fetuses; treatment at the higher dose level resulted in the

death of 5/11 pregnant monkeys with 3/11 animals aborting their fetuses; reduced food consumption and diarrhea were observed in all animals during the treatment period; no indication of teratogenic potential; maternal < 10 mg/kg/day (excessive abortions), developmental NOEL  $\geq$  50 mg/kg/day (no effect at HDT); lack of dosing solution analysis to confirm the actual dosage administered and control group; originally reviewed as unacceptable but possibly upgradeable with additional data to eliminate the deficiencies mentioned above; (Leung, 12/9/92). subsequently reviewed with dosing solution analyses and historical control data; **supplemental**; (revised, Leung, 3/5/93).

### Gene Mutation

\*\*51910-030; 114482; "Study of the Mutagenic Potential of the Compound Hoe 33171 O H AS201 in Strains of *Salmonella typhimurium* (Ames Test) and *Escherichia coli*"; 842; Dept. of Toxicology, Hoechst AG, Frankfurt/Main, Germany; report #432/82; 8/2/82; Hoe 33171 O H AS201 (fenoxaprop-ethyl); TGAI; *S. typhimurium* strains TA 98, 100, 1535, 1537, & 1538 - assay: reversion to histidine prototrophy; *E. coli* strain WP2 uvrA - assay: reversion to tryptophan prototrophy; dosing (determined by a preliminary cytotoxicity test): 0, 4, 20, 100, 500, 2500, & 5000  $\mu$ g/plate  $\pm$  Aroclor 1254-induced S9 rat liver activating microsomes; 48-72 hr @ 37°C; positive controls demonstrated mutability of all strains; no test article-dependent increase in revertants at any dose, thus, no mutagenic activity; **Acceptable**. (Rubin, 11/5/92)

51910-030; 114483; "Test for Mutagenicity in Bacteria Strains in the Absence and Presence of a Liver Preparation" (author: Dr. Engelbart); 842; Arbeitsgruppe Molekularbiologie, Hoechst, Frankfurt, Germany; report #47/79; 7/9/79; Hoe 33171 OH AT 203 (fenoxaprop-ethyl); TGAI; *S. typhimurium* strains TA 98, 100, 1535, & 1537; - assay: reversion to histidine prototrophy; dosing: 0, 4, 20, 100, 500, 1500 (w/o S9 only), & 2500 (+S9 only)  $\mu$ g/plate  $\pm$  Aroclor 1254-induced S9 rat liver activating microsomes; 48 hr @ 37°C; no evidence of cytotoxicity; positive controls demonstrated mutability of all strains; no test article-dependent increase in revertants at any dose, thus, no mutagenic activity; **Unacceptable, not upgradeable** (limit dose was not used, no evidence of cytotoxicity at the high dose). (Rubin, 11/6/92)

\*\*51910-030; 114484; "Study of the Mutagenic Activity "In Vitro" of the Compound Hoe 33171 OH AS 201 with *Schizosaccharomyces pombe*" (study director: Diego Mellano); 842; Instituto di Ricerche Biomediche, Torino, Italy; study #M 417; 9/10/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; *S. pombe* haploid mutant yeast (SP ade 6-60/rad 10-198, h-); dosing ( $\pm$  Aroclor 1254-induced S9 rat liver activating microsomes): 0, 125, 250, 500, 1000  $\mu$ g/ml; relative survival @ 1000  $\mu$ g/dose = 51.95% (-S9) and 88.36% (+S9); 4-hr exposure to test article @ 35°C followed by plating in agar @ 32°C for 5 days (mutation detected by appearance of white colonies); positive controls demonstrated mutability; no test article-dependent increase in the proportion of white colonies, thus, no mutagenic activity; **Acceptable**; (Rubin 11/6/92)

### Chromosome Effects

\*\*51910-030; 114485; "Study of the Capacity of the Test Article Hoe 33171 OH AS 201 to Induce Chromosome Aberrations in Human Lymphocytes Cultured *In vitro*" (Study Director: Diego Mellano); 843; Instituto di Ricerche Biomediche, Torino, Italy; study #M 419; 12/23/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; lymphocytes freshly isolated from a male

volunteer; dosing ( $\pm$  Aroclor 1254-induced S9 rat liver activating microsomes): 0, 1, 10, 100, 1000  $\mu\text{g}/\text{ml}$ ; 3 hr exposure @ 37°C; cells arrested at metaphase in colchicine; apprx. 100 metaphases/dose were examined; cytotoxicity evident @ 1000  $\mu\text{g}/\text{ml}$  by >80% decline in the # of metaphases; positive controls demonstrated susceptibility to induced chromosome aberrations; no test article dependent increase in chromosome aberrations, thus, no clastogenic activity under the conditions tested; **Acceptable**. (Rubin, 11/6/92)

51910-030; 114486; "Micronucleus Test in Male and Female NMR1 Mice Following Oral Administration" (Study Directors: Drs. Leist & Jung); 843; Hoechst Aktiengesellschaft, Frankfurt, Germany; study # 689/81; 9/19/84; Hoe 33171 OH AT 204 (fenoxaprop-ethyl); 93% purity; NMR1 mice; animals dosed twice by gavage, first @ 0 hr, then @ 24 hr, then sacrificed @ 30 hr (6 hr after the second dosing); doses: 0, 18, 180, & 1800 mg/kg; 5/sex/dose; positive controls with Endoxan (100 mg/kg) demonstrated susceptibility both to induced micronucleus formation in polychromatic cells and to altered polychromatic-to-normochromatic cell ratio; no test article dependent increase in micronucleus formation or change in cell ratio was observed, thus, no clastogenic activity, mitotic spindle disruption, or changes in cell dynamics in the bone marrow occurred under the conditions tested; **Unacceptable** (guidelines require at least 3 time points at the highest dose with none starting earlier than 12 hr after the second application of test article). (Rubin, 11/9/92)

#### DNA Damage

51910-030; 114487; "Study of the Mutagenic Activity of the Compound Hoe 33171 OH AS 201 with *Saccharomyces cerevisiae*" (Study Director: Diego Mellano); 843; *S. cerevisiae* strain D4; Instituto di Ricerche Biomediche, Torino, Italy; study #M 416; 9/13/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; doses ( $\pm$  Aroclor 1254-induced rat liver S9 activating microsomes): 0, 125, 250, 500, & 1000  $\mu\text{g}/\text{ml}$ ; 4 hr test article exposure; positive controls: cyclophosphamide (258  $\mu\text{g}/\text{mg}$ , +S9 only) and methyl methane sulfonate (84.5  $\mu\text{g}/\text{ml}$ , w/o S9 only); experimental incubations contained 2.5% DMSO, positive controls contained no DMSO; mitotic gene conversion either to tryptophan or adenine prototrophy not observed despite evidence for increasing toxicity with dose; **Unacceptable** (positive control data are not comparable to test article data because of disparity in DMSO concentration). (Rubin, 11/9/92)

51910-030; 114488; "Study of the Capacity of the Test Article Hoe 33171 OH AS 201 to Induce "Unscheduled DNA Synthesis" [UDS] in Cultured HeLa Cells" (Study Director: Diego Mellano); 844; Instituto di Ricerche Biomediche, Torino, Italy; study #M 418; 10/10/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; doses ( $\pm$  Aroclor 1254-induced S9 rat liver activating microsomes): 5, 50, & 500  $\mu\text{g}/\text{ml}$ ; 1 hr test article exposure followed by 3 hr exposure to 1  $\mu\text{Ci}/\text{ml}$   $^3\text{H}$ -thymidine; positive controls: methyl methane sulfonate (1 mM, w/o S9 only) and cyclophosphamide (1.38 mM, +S9 only); UDS assays done in the presence of hydroxyurea (HU=10 mM) to inhibit S-phase DNA synthesis; cytotoxicity test (measured in the absence of HU): high dose of test article inhibited DNA synthesis by 93%, mid-high dose by 31% w/o S9; HU inhibited DNA synthesis in controls by 98% and 97% (+ & - S9); test article did not induce any increase in DNA synthesis in the presence of HU either + or - S9 (positive controls increased synthesis by apprx. 2-fold), thus it apparently does not cause an increase in repair synthesis; **Unacceptable** (positive control data in the presence of HU are too weak to permit interpretation of test article data). (Rubin, 11/10/92)

\*\* 065; 121153; "Unscheduled DNA Synthesis in Hepatocytes of Male Rats In Vitro with HOE 331171 OH ZD 98 0001" (Authors: Miltenburger, H.G., et. al., Cytotest Cell Research Gmbh & Co. KG, Darmstadt, Germany, Test Report Project # CCR 100800, 2/19/87); 844; HOE 33171 OH ZD 98 0001 (Batch # 13982, 96.5% purity); tested in primary Wistar CF HB rat hepatocyte cultures; two separate trials; 6 replicates/dose; concentrations of 0, 1, 3.33, 10, 33.33, and 100 ug/ml; 3 hour exposure to test article and <sup>3</sup>H-Tdr; UDS determined by liquid scintillation counting; UDS assay performed in the presence of hydroxyurea (15 mM) to inhibit S-phase DNA synthesis; positive controls functional; **no adverse effect**; test article did not induce DNA repair in the hepatocytes used; **acceptable**; (Leung, 3/8/93).

CONCLUSIONS: Do data support registration?

Toxicity data for Whip IEC Herbicide and the active ingredient, fenoxaprop ethyl, were submitted and reviewed.

Separate acute oral toxicity studies conducted with the TGAI using only male or female rats were unacceptable and not upgradeable, but when considered collectively, contained sufficient information to support a toxicity category III. Although, the acute dermal toxicity study using the TGAI is unacceptable and not upgradeable, the 21-day dermal toxicity study provides enough information to support a toxicity category III. Other acute studies with the TGAI, including the inhalation toxicity and primary eye and dermal irritation studies are acceptable.

Individual acute oral and dermal toxicity studies conducted with the formulated product employing males or females are not acceptable and not upgradeable, but collectively provide sufficient information to support a toxicity category III. The acute inhalation toxicity and the primary eye and dermal irritation studies with the formulated product are acceptable. Product label identifies all potential hazards indicated by the data reviewed.

Although the individual metabolism studies are unacceptable, collectively, data from all seven studies provide adequate information to fulfill the requirements for an acceptable animal metabolism study.

Acceptable subchronic studies employing oral, dermal, and inhalation routes of administration have been submitted. Results from these studies have established the liver as a potential target.

Dose levels employed in the chronic studies did not produce any effects. However, the dose levels selected were justified by the subchronic studies (see below) where adaptation to the test article exposure was evident.

#### Oral

90-day study in rats (#114442): 0, 20, 80, and 320 ppm; 320 ppm - elevated alkaline phosphatase in males, enlargement of centrilobular hepatocytes and fine eosinophilic granulation of the cytoplasm (these changes were reversible during a 4-week recovery period; NOEL = 80 ppm

- 32-day range-finding study in rats (#114441): 0, 80, 315, 1250, and 5000 ppm; 5000 ppm - rats killed in extremis on day 8; 1250 ppm - elevated alkaline phosphatase; 315 ppm - eosinophilic cytoplasm and enlarged hepatocytes; NOEL = 80 ppm
- 30-day study in dogs (#114445): 0, 80, 400, and 2000 ppm; 2000 ppm - dogs killed in extremis; 400 ppm - liver degeneration, elevated alkaline phosphatase, relative histopathological effect consistent with 2000 ppm seen in 1 dog; 80 ppm - nothing treatment-related apparent; NOEL = 80 ppm
- 90-day study in dogs (#114446): 0, 16, 80, and 400 ppm; 400 and 80 ppm - either induced or promoted "chronic interstitial pyelonephritis"; NOEL = 16 ppm
- 2-year dog study (#114458): 0, 3, 15, and 75 ppm; 75 ppm - decreased body weight gain, about 50% of control; no evidence of pyelonephritis; NOEL = 15 ppm
- 32-day mouse study (#114443): 0, 80, 315, 1250, and 5000 ppm; 5000 and 1250 ppm - mice killed in extremis; 315 ppm - elevated SGPT and alkaline phosphatase, enlarged hepatocytes and renal tubule lesions, also to a lesser degree at 80 ppm; NOEL < 80 ppm
- 30 - day mouse study (#114444): 0, 5, 10, 20, and 80 ppm; 80 and 20 ppm - enlarged hepatic epithelia, eosinic hepatocytes, no necrosis, no increase in alkaline phosphatase; NOEL = 10 ppm
- 2-year mouse study (#114461): 0, 2.5, 10, and 40 ppm; no treatment-related chronic-type effects; NOEL = 40 ppm

The chronic feeding study in rats is acceptable. The chronic toxicity conducted in dogs has been upgraded to acceptable status with the submission of test diet analyses to confirm the actual concentrations of HOE 33171. Combined chronic toxicity/carcinogenicity study in rats and the carcinogenicity study in mice are acceptable. In the latter study, ovarian papillary cystadenomata was considered with the incidence of cysts lined by hyperplastic epithelium. Both lesions are characterized by a cyst lined by proliferative epithelium with differential diagnosis depending on the presence of a papillary projection into the cystic cavity. When both proliferative lesions were considered together no treatment-related effect was observed.

The teratology study conducted in rats has been upgraded to acceptable status, whereas the other teratology study in mice remains unacceptable but possibly upgradeable upon submission of dosing solution analyses to confirm the actual amounts of test material administered. By considering both rabbit teratology studies together, the number of fetuses examined for visceral and skeletal abnormalities is adequate and with the submission of dosing solution analyses, both rabbit teratology studies have been upgraded to acceptable status. Another rabbit teratology study where the test material was applied dermally is unacceptable but possibly upgradeable with submission of dose solution analyses. An oral embryotoxicity study in the cynomolgus monkey was not submitted as a guideline study but provides supplemental information.

One of the two rat reproductive toxicity studies is acceptable.

Studies were submitted to fulfill the data requirements for gene mutation, structural chromosomal aberration and other genotoxic effects categories are acceptable.

Acute toxicity data have been reviewed for acute dietary assessment purposes and a NOEL for fenoxaprop ethyl was determined to be 400 ppm (29.4 and 24.3 mg/kg/day for males and females, respectively). Dogs treated at higher doses (2000 ppm) in a range-finding study had to be killed in moribund state on days 3 and 5 of the study. Clinical signs demonstrated at this dose level consisted of asynchronism and general weakness. In addition, dams from a rat teratology study exhibited signs of toxicity including abortions and slightly impaired fetal growth at 100 mg/kg/day. However, repeated dosing at 32 and 10 mg/kg/day did not exert any effects.

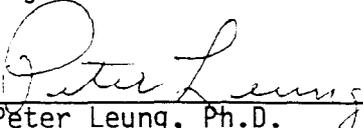
RECOMMENDATIONS: What type of registration action is being considered? In the case of ongoing registration, register or do not register? What other specific studies or data are requested?

Submitted as a new active ingredient Section 3 registration request.

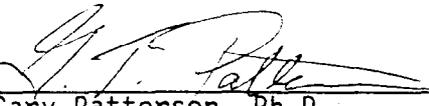
The data are adequate to make a complete toxicological evaluation of the subject product.

Product label identifies all potential acute hazards indicated by the data reviewed.

Registration is recommended.

  
\_\_\_\_\_  
Peter Leung, Ph.D.  
Staff Toxicologist

3/16/94  
Date

  
\_\_\_\_\_  
Gary Patterson, Ph.D.  
Senior Toxicologist

3/16/94  
Date

  
\_\_\_\_\_  
Joyce Gee, Ph.D.  
Senior Toxicologist

3/16/94  
Date

**APPENDIX B  
DIETARY EXPOSURE ASSESSMENT**

**RESIDUE FILE**

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 Acute Exposure (EX4) Analysis for Fenoxaprop-Ethyl;                   Section 3 Registration  
 RESIDUE FILE NAME: FNRICE1A (NFCS87/88 DATA)                   ANALYSIS DATE: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 COMMENT 1: Registrant field residue data, MDL for acute nondetects  
 COMMENT 2: California rice labeled use  
 -----

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE <sup>1</sup> CODE
270	0	RICE-ROUGH (BROWN)	0.020000	1.00	1.00	REG-f
271	0	RICE-MILLED (WHITE)	0.020000	1.00	1.00	REG-f
408	0	RICE-BRAN	0.020000	1.00	1.00	REG-f

1/   REG-f =       Registrant supplied field residue data.

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICE1A (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 COMMENT 1: Registrant residue data, nondetects = MDL of 0.02 ppm  
 COMMENT 2: California labeled use for rice  
 Initial estimate of user-days as % of person-days in survey = 49.00%  
 -----

U.S. POP - ALL SEASONS  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
27.6%	0.000014	0.000023	0.000000	692455

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000022	449,075
80.0	0.000001	>1,000,000	10.0	0.000035	282,998
70.0	0.000003	>1,000,000	5.0	0.000050	198,405
60.0	0.000004	>1,000,000	2.5	0.000071	141,519
50.0	0.000007	>1,000,000	1.0	0.000100	100,237
40.0	0.000011	934,653	0.5	0.000145	68,971
30.0	0.000015	654,070	0.0	0.000409	24,423

WESTERN REGION  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
29.3%	0.000014	0.000019	0.000000	712412

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000023	439,843
80.0	0.000001	>1,000,000	10.0	0.000037	270,907
70.0	0.000002	>1,000,000	5.0	0.000049	205,578
60.0	0.000004	>1,000,000	2.5	0.000066	152,667
50.0	0.000008	>1,000,000	1.0	0.000084	119,340
40.0	0.000011	872,948	0.5	0.000109	91,769
30.0	0.000016	628,413	0.0	0.000219	45,585

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICELA (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

HISPANICS  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
40.5%	0.000024	0.000024	0.000001	409897

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000003	>1,000,000	20.0	0.000040	247,887
80.0	0.000006	>1,000,000	10.0	0.000059	170,785
70.0	0.000010	982,136	5.0	0.000075	132,462
60.0	0.000014	705,972	2.5	0.000084	119,675
50.0	0.000018	563,036	1.0	0.000093	106,987
40.0	0.000021	469,662	0.5	0.000109	91,732
30.0	0.000028	362,505	0.0	0.000207	48,287

NON-HISPANIC WHITES  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
25.6%	0.000011	0.000015	0.000000	938368

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000017	575,213
80.0	0.000001	>1,000,000	10.0	0.000027	366,832
70.0	0.000002	>1,000,000	5.0	0.000038	266,664
60.0	0.000004	>1,000,000	2.5	0.000048	206,840
50.0	0.000005	>1,000,000	1.0	0.000068	146,886
40.0	0.000008	>1,000,000	0.5	0.000084	119,077
30.0	0.000012	852,137	0.0	0.000263	38,079

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICE1A (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

NON-HISPANIC BLACKS  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
34.3%	0.000021	0.000033	0.000001	476273

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000030	329,512
80.0	0.000002	>1,000,000	10.0	0.000044	227,125
70.0	0.000004	>1,000,000	5.0	0.000064	156,506
60.0	0.000008	>1,000,000	2.5	0.000092	108,749
50.0	0.000013	748,979	1.0	0.000187	53,587
40.0	0.000018	562,644	0.5	0.000231	43,207
30.0	0.000022	446,804	0.0	0.000366	27,351

NON-HISPANIC OTHER  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
38.5%	0.000044	0.000048	0.000003	225126

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000069	144,561
80.0	0.000011	886,952	10.0	0.000097	103,176
70.0	0.000019	524,104	5.0	0.000144	69,601
60.0	0.000022	458,255	2.5	0.000173	57,888
50.0	0.000029	346,714	1.0	0.000230	43,429
40.0	0.000038	265,544	0.5	0.000288	34,705
30.0	0.000051	194,350	0.0	0.000409	24,423

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICE1A (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

NURSING INFANTS (<1 YEAR)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			Margin of Safety 1/
	Mean	Standard Deviation	Standard Error	
40.2%	0.000030	0.000023	0.000004	338182

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000003	>1,000,000	20.0	0.000052	191,030
80.0	0.000005	>1,000,000	10.0	0.000059	169,453
70.0	0.000010	964,258	5.0	0.000064	156,403
60.0	0.000016	633,495	2.5	0.000069	145,697
50.0	0.000023	433,808	1.0	0.000071	139,950
40.0	0.000032	308,561	0.5	0.000072	138,133
30.0	0.000047	212,887	0.0	0.000073	136,364

NON-NURSING INFANTS (<1)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			Margin of Safety 1/
	Mean	Standard Deviation	Standard Error	
48.5%	0.000048	0.000066	0.000005	209245

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000006	>1,000,000	20.0	0.000058	173,775
80.0	0.000007	>1,000,000	10.0	0.000093	107,845
70.0	0.000011	880,374	5.0	0.000233	42,956
60.0	0.000016	620,431	2.5	0.000243	41,114
50.0	0.000027	365,467	1.0	0.000249	40,083
40.0	0.000038	261,222	0.5	0.000252	39,750
30.0	0.000048	208,734	0.0	0.000263	38,079

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICE1A (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

FEMALES (13+/PREG/NOT NSG)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
17.5%	0.000011	0.000013	0.000002	894161

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	>1,000,000	20.0	0.000018	562,443
80.0	0.000001	>1,000,000	10.0	0.000024	409,157
70.0	0.000004	>1,000,000	5.0	0.000030	338,015
60.0	0.000007	>1,000,000	2.5	0.000044	227,236
50.0	0.000008	>1,000,000	1.0	0.000060	165,983
40.0	0.000008	>1,000,000	0.5	0.000074	134,304
30.0	0.000014	731,637	0.0	0.000089	111,999

FEMALES (13+/NURSING)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
28.4%	0.000018	0.000016	0.000003	551993

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000022	464,238
80.0	0.000010	>1,000,000	10.0	0.000034	295,524
70.0	0.000012	809,640	5.0	0.000047	212,504
60.0	0.000014	716,435	2.5	0.000057	176,223
50.0	0.000015	661,670	1.0	0.000079	126,942
40.0	0.000016	623,432	0.5	0.000091	110,424
30.0	0.000019	530,830	0.0	0.000102	97,710

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICE1A (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

CHILDREN (1-6 YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
28.9%	0.000025	0.000037	0.000001	393104

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000038	262,073
80.0	0.000002	>1,000,000	10.0	0.000065	153,139
70.0	0.000004	>1,000,000	5.0	0.000090	111,002
60.0	0.000009	>1,000,000	2.5	0.000120	83,028
50.0	0.000015	685,052	1.0	0.000161	61,940
40.0	0.000020	508,343	0.5	0.000231	43,284
30.0	0.000026	388,313	0.0	0.000409	24,423

CHILDREN (7-12 YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
29.7%	0.000019	0.000025	0.000001	514628

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000031	326,961
80.0	0.000001	>1,000,000	10.0	0.000049	202,327
70.0	0.000003	>1,000,000	5.0	0.000074	135,484
60.0	0.000006	>1,000,000	2.5	0.000093	107,250
50.0	0.000011	931,354	1.0	0.000108	92,294
40.0	0.000018	551,774	0.5	0.000140	71,527
30.0	0.000023	443,547	0.0	0.000233	42,907

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICE1A (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

-----  
 MALES (13-19 YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
26.2%	0.000016	0.000020	0.000001	633011

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000024	417,892
80.0	0.000001	>1,000,000	10.0	0.000038	263,982
70.0	0.000002	>1,000,000	5.0	0.000051	195,494
60.0	0.000007	>1,000,000	2.5	0.000077	129,904
50.0	0.000012	843,976	1.0	0.000085	117,184
40.0	0.000015	659,744	0.5	0.000103	97,046
30.0	0.000018	550,292	0.0	0.000201	49,682

-----  
 FEMALES (13-19 YRS/NP/NN)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
27.6%	0.000013	0.000016	0.000001	754666

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	>1,000,000	20.0	0.000024	410,642
80.0	0.000001	>1,000,000	10.0	0.000035	287,861
70.0	0.000002	>1,000,000	5.0	0.000043	233,212
60.0	0.000004	>1,000,000	2.5	0.000057	174,889
50.0	0.000008	>1,000,000	1.0	0.000064	156,171
40.0	0.000012	838,772	0.5	0.000073	137,306
30.0	0.000017	604,128	0.0	0.000178	56,240

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICELA (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

-----  
 MALES (20+ YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
30.4%	0.000011	0.000015	0.000000	932711

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000017	578,564
80.0	0.000002	>1,000,000	10.0	0.000027	375,703
70.0	0.000002	>1,000,000	5.0	0.000038	261,511
60.0	0.000004	>1,000,000	2.5	0.000051	196,519
50.0	0.000005	>1,000,000	1.0	0.000066	152,597
40.0	0.000008	>1,000,000	0.5	0.000086	116,937
30.0	0.000011	881,324	0.0	0.000263	37,996

-----  
 FEMALES (20+ YEARS/NP/NN)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
24.0%	0.000012	0.000015	0.000000	862853

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	>1,000,000	20.0	0.000019	526,548
80.0	0.000001	>1,000,000	10.0	0.000029	347,625
70.0	0.000003	>1,000,000	5.0	0.000038	261,867
60.0	0.000004	>1,000,000	2.5	0.000050	201,176
50.0	0.000006	>1,000,000	1.0	0.000072	138,635
40.0	0.000009	>1,000,000	0.5	0.000094	106,559
30.0	0.000013	761,209	0.0	0.000170	58,837

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNRICE1A (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

CUSTOM DEMOGRAPHICS 1: Seniors 55+ Years  
 All Seasons All Regions Sex: M F-all  
 All Races Age-Low: 55 yrs High: 110 yrs  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
25.4%	0.000009	0.000011	0.000000	>1000000

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000001	>1,000,000	20.0	0.000014	697,542
80.0	0.000001	>1,000,000	10.0	0.000022	453,053
70.0	0.000002	>1,000,000	5.0	0.000030	336,242
60.0	0.000004	>1,000,000	2.5	0.000038	262,706
50.0	0.000006	>1,000,000	1.0	0.000051	195,772
40.0	0.000008	>1,000,000	0.5	0.000075	132,862
30.0	0.000010	976,123	0.0	0.000097	103,353

1/ Margin of Safety = DPR NOEL ÷ Dietary Exposure

Acute Exposure (EX4) Analysis for Fenoxaprop-Ethyl; Section 3 Registration  
 RESIDUE FILE NAME: FNALLIAC (NFCS87/88 DATA) ANALYSIS DATE: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 COMMENT 1: Registrant field residue data, MDL for acute nondetects  
 COMMENT 2: California rice labeled use

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE <sup>1</sup> CODE
239	A	PEANUTS-WHOLE	no consumption in survey			
255	G	SOYBEANS-SPROUTED SEEDS	0.050000	0.33	1.00	REG
265	O	BARLEY	0.050000	1.00	1.00	REG
270	O	RICE-ROUGH (BROWN)	0.020000	1.00	1.00	REG-f
271	O	RICE-MILLED (WHITE)	0.020000	1.00	1.00	REG-f
276	O	WHEAT-ROUGH	0.050000	1.00	1.00	REG
277	O	WHEAT-GERM	0.050000	1.00	1.00	REG
278	O	WHEAT-BRAN	0.050000	1.00	1.00	REG
279	O	WHEAT-FLOUR	0.050000	1.00	1.00	REG
290	A	COTTONSEED-OIL	0.050000	1.00	1.00	REG
291	A	COTTONSEED-MEAL	0.050000	1.00	1.00	REG
293	A	PEANUTS-OIL	0.050000	1.00	1.00	REG
297	G	SOYBEANS-OIL	0.050000	1.00	1.00	REG
303	G	SOYBEANS-UNSPECIFIED	0.050000	1.00	1.00	REG
304	G	SOYBEANS-MATURE SEEDS DRY	0.050000	1.00	1.00	REG
305	G	SOYBEANS-FLOUR (FULL FAT)	0.050000	1.00	1.00	REG
306	G	SOYBEANS-FLOUR (LOW FAT)	0.050000	1.00	1.00	REG
307	G	SOYBEANS-FLOUR (DEFATTED)	0.050000	1.00	1.00	REG
318	X	MILK-NONFAT SOLIDS	0.010000	1.00	1.00	REG
319	X	MILK-FAT SOLIDS	0.010000	1.00	1.00	REG
320	X	MILK SUGAR (LACTOSE)	0.010000	1.00	1.00	REG
321	U	BEEF-MEAT BYPRODUCTS	0.010000	1.00	1.00	REG-m
323	U	BEEF-DRIED	0.010000	1.92	1.00	REG-m
324	U	BEEF(BONELESS)-FAT	0.010000	1.00	1.00	REG-m
327	U	BEEF(BONELESS)-LEAN (FAT/FREE)	0.010000	1.00	1.00	REG-m
328	U	GOAT-MEAT BYPRODUCTS	no consumption in survey			
330	U	GOAT(BONELESS)-FAT	no consumption in survey			
333	U	GOAT(BONELESS)-LEAN (FAT/FREE)	no consumption in survey			
334	U	HORSE	no consumption in survey			
336	U	SHEEP-MEAT BYPRODUCTS	no consumption in survey			
338	U	SHEEP(BONELESS)-FAT	0.050000	1.00	1.00	REG
341	U	SHEEP(BONELESS)-LEAN (FAT FREE)	0.050000	1.00	1.00	REG
342	U	PORK-MEAT BYPRODUCTS	0.050000	1.00	1.00	REG
344	U	PORK(BONELESS)-FAT	0.050000	1.00	1.00	REG
347	U	PORK(BONELESS)-LEAN (FAT FREE)	0.050000	1.00	1.00	REG
398	X	MILK-BASED WATER	0.010000	1.00	1.00	REG
403	A	PEANUT-BUTTER	0.050000	1.89	1.00	REG

-----  
 Acute Exposure (EX4) Analysis for Fenoxaprop-Ethyl;                   Section 3 Registration  
 RESIDUE FILE NAME: FNALL1AC (NFCS87/88 DATA)                   ANALYSIS DATE: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

RESIDUE FILE LISTING (continued)

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
408	O	RICE-BRAN	no consumption in survey			
424	U	VEAL-(BONELESS)-FAT	0.010000	1.00	1.00	REG-m
425	U	VEAL-(BONELESS)-LEAN (FAT FREE)	0.010000	1.00	1.00	REG-m
429	U	VEAL-DRIED	no consumption in survey			
430	U	VEAL-MEAT BYPRODUCTS	no consumption in survey			
437	O	WHEAT-GERM OIL	0.050000	1.00	1.00	REG
940	A	PEANUTS HULLED	0.050000	1.00	1.00	REG

1/   REG   =   Registrant supplied data.  
       REG-f =   Registrant supplied field residue data.  
       REG-m =   Registrant supplied metabolism and dietary data.

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALLIAC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 COMMENT 1: Registrant residue data, nondetects = MDL of 0.02 ppm  
 COMMENT 2: California and federal labeled uses  
 Initial estimate of user-days as % of person-days in survey = 100.00%  
 -----

U.S. POP - ALL SEASONS  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.9%	0.000209	0.000193	0.000001	47761

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000059	169,085	20.0	0.000289	34,625
80.0	0.000084	118,445	10.0	0.000427	23,402
70.0	0.000106	94,053	5.0	0.000590	16,935
60.0	0.000129	77,759	2.5	0.000749	13,345
50.0	0.000153	65,364	1.0	0.000965	10,367
40.0	0.000183	54,666	0.5	0.001122	8,913
30.0	0.000224	44,700	0.0	0.003165	3,159

WESTERN REGION  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.9%	0.000215	0.000193	0.000003	46598

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000060	166,666	20.0	0.000303	33,009
80.0	0.000084	118,444	10.0	0.000438	22,845
70.0	0.000108	92,762	5.0	0.000589	16,980
60.0	0.000131	76,067	2.5	0.000746	13,407
50.0	0.000158	63,229	1.0	0.000978	10,225
40.0	0.000191	52,334	0.5	0.001160	8,617
30.0	0.000233	42,929	0.0	0.002411	4,147

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALLIAC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

HISPANICS  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.4%	0.000203	0.000181	0.000005	49321

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000051	197,539	20.0	0.000292	34,238
80.0	0.000069	145,587	10.0	0.000434	23,067
70.0	0.000091	109,312	5.0	0.000609	16,421
60.0	0.000119	84,379	2.5	0.000729	13,715
50.0	0.000147	67,858	1.0	0.000899	11,120
40.0	0.000184	54,354	0.5	0.000997	10,026
30.0	0.000221	45,250	0.0	0.001089	9,184

NON-HISPANIC WHITES  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.9%	0.000209	0.000185	0.000001	47928

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000062	160,589	20.0	0.000284	35,196
80.0	0.000088	113,813	10.0	0.000421	23,770
70.0	0.000109	92,066	5.0	0.000584	17,130
60.0	0.000130	76,713	2.5	0.000740	13,515
50.0	0.000154	64,941	1.0	0.000966	10,352
40.0	0.000183	54,682	0.5	0.001132	8,831
30.0	0.000222	45,016	0.0	0.002411	4,147

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALLLAC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

NON-HISPANIC BLACKS  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
100.0%	0.000206	0.000234	0.000004	48536

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000047	214,700	20.0	0.000297	33,703
80.0	0.000067	149,750	10.0	0.000436	22,936
70.0	0.000088	114,066	5.0	0.000620	16,118
60.0	0.000114	87,896	2.5	0.000768	13,013
50.0	0.000139	71,828	1.0	0.000962	10,396
40.0	0.000169	59,071	0.5	0.001055	9,482
30.0	0.000221	45,210	0.0	0.003165	3,159

NON-HISPANIC OTHER  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
100.0%	0.000249	0.000217	0.000008	40130

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000062	161,521	20.0	0.000376	26,621
80.0	0.000088	113,828	10.0	0.000484	20,653
70.0	0.000122	82,293	5.0	0.000627	15,945
60.0	0.000150	66,843	2.5	0.000844	11,849
50.0	0.000190	52,566	1.0	0.001076	9,297
40.0	0.000230	43,556	0.5	0.001282	7,763
30.0	0.000306	32,644	0.0	0.001999	5,003

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALLIAC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

NURSING INFANTS (<1 YEAR)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
98.2%	0.000142	0.000169	0.000020	70364

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000019	515,668	20.0	0.000171	58,594
80.0	0.000063	159,962	10.0	0.000278	35,956
70.0	0.000081	123,438	5.0	0.000356	28,077
60.0	0.000087	114,969	2.5	0.000765	13,066
50.0	0.000092	109,167	1.0	0.000978	10,225
40.0	0.000096	103,898	0.5	0.000998	10,022
30.0	0.000134	74,504	0.0	0.001018	9,826

NON-NURSING INFANTS (<1)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.4%	0.000419	0.000346	0.000019	23880

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000166	60,333	20.0	0.000563	17,768
80.0	0.000190	52,623	10.0	0.000957	10,450
70.0	0.000215	46,423	5.0	0.001046	9,561
60.0	0.000246	40,725	2.5	0.001187	8,422
50.0	0.000303	32,969	1.0	0.001854	5,393
40.0	0.000360	27,748	0.5	0.002139	4,675
30.0	0.000423	23,622	0.0	0.002411	4,147

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALLIAC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

FEMALES (13+/PREG/NOT NSG)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.6%	0.000154	0.000085	0.000005	65111

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000061	163,464	20.0	0.000213	46,865
80.0	0.000083	120,756	10.0	0.000256	39,043
70.0	0.000106	94,141	5.0	0.000289	34,599
60.0	0.000121	82,548	2.5	0.000363	27,519
50.0	0.000147	68,133	1.0	0.000465	21,523
40.0	0.000158	63,286	0.5	0.000513	19,496
30.0	0.000178	56,164	0.0	0.000595	16,819

FEMALES (13+/NURSING)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
100.0%	0.000171	0.000088	0.000007	58412

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000092	108,860	20.0	0.000227	44,149
80.0	0.000114	87,713	10.0	0.000265	37,763
70.0	0.000127	78,643	5.0	0.000326	30,674
60.0	0.000139	71,829	2.5	0.000398	25,099
50.0	0.000152	65,895	1.0	0.000488	20,499
40.0	0.000171	58,379	0.5	0.000552	18,111
30.0	0.000194	51,613	0.0	0.000674	14,832

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALLIAC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

CHILDREN (1-6 YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
100.0%	0.000564	0.000306	0.000006	17723

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000266	37,620	20.0	0.000754	13,255
80.0	0.000329	30,393	10.0	0.000925	10,808
70.0	0.000388	25,741	5.0	0.001091	9,170
60.0	0.000457	21,873	2.5	0.001239	8,070
50.0	0.000517	19,353	1.0	0.001513	6,610
40.0	0.000577	17,331	0.5	0.001775	5,634
30.0	0.000656	15,237	0.0	0.003165	3,159

CHILDREN (7-12 YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
100.0%	0.000355	0.000195	0.000004	28141

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000145	69,155	20.0	0.000492	20,345
80.0	0.000198	50,608	10.0	0.000608	16,455
70.0	0.000240	41,624	5.0	0.000721	13,875
60.0	0.000279	35,820	2.5	0.000825	12,117
50.0	0.000322	31,037	1.0	0.000998	10,021
40.0	0.000367	27,217	0.5	0.001151	8,688
30.0	0.000421	23,771	0.0	0.001612	6,203

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALLLAC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

-----  
 MALES (13-19 YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
100.0%	0.000222	0.000114	0.000003	45000

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000092	108,305	20.0	0.000310	32,275
80.0	0.000124	80,556	10.0	0.000382	26,198
70.0	0.000150	66,783	5.0	0.000429	23,314
60.0	0.000175	57,235	2.5	0.000491	20,358
50.0	0.000205	48,827	1.0	0.000561	17,820
40.0	0.000238	42,021	0.5	0.000623	16,060
30.0	0.000270	37,094	0.0	0.001020	9,808

-----  
 FEMALES (13-19 YRS/NP/NN)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
100.0%	0.000185	0.000116	0.000003	54134

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000064	157,139	20.0	0.000255	39,191
80.0	0.000095	105,215	10.0	0.000325	30,793
70.0	0.000118	84,586	5.0	0.000382	26,164
60.0	0.000140	71,491	2.5	0.000442	22,616
50.0	0.000166	60,321	1.0	0.000607	16,468
40.0	0.000190	52,611	0.5	0.000657	15,230
30.0	0.000221	45,262	0.0	0.001834	5,452

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALL1AC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

MALES (20+ YEARS)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.9%	0.000155	0.000095	0.000001	64456

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000059	168,622	20.0	0.000216	46,195
80.0	0.000082	122,172	10.0	0.000273	36,595
70.0	0.000100	99,878	5.0	0.000329	30,414
60.0	0.000119	84,319	2.5	0.000387	25,852
50.0	0.000137	73,100	1.0	0.000502	19,927
40.0	0.000157	63,632	0.5	0.000579	17,257
30.0	0.000182	54,979	0.0	0.001089	9,182

FEMALES (20+ YEARS/NP/NN)  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			
	Mean	Standard Deviation	Standard Error	Margin of Safety 1/
99.8%	0.000130	0.000078	0.000001	76919

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
(in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000046	215,423	20.0	0.000184	54,306
80.0	0.000066	151,981	10.0	0.000233	42,971
70.0	0.000083	120,126	5.0	0.000281	35,646
60.0	0.000099	100,659	2.5	0.000325	30,777
50.0	0.000116	86,453	1.0	0.000382	26,192
40.0	0.000134	74,636	0.5	0.000423	23,645
30.0	0.000155	64,360	0.0	0.001559	6,413

-----  
 ACUTE EXPOSURE (EX4) ANALYSIS FOR FENOXAPROP-ETHYL; Section 3 Registration  
 Residue file name: FNALL1AC (NFCS87/88 DATA) Analysis date: 03-02-1994  
 DPR NOEL (Acute) = 10.0 mg/kg body-wt/day  
 -----

CUSTOM DEMOGRAPHICS 1: Seniors 55+ Years  
 All Seasons All Regions Sex: M F-all  
 All Races Age-Low: 55 yrs High: 110 yrs  
 -----

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY (mg/kg body wt/day)			Margin of Safety 1/
	Mean	Standard Deviation	Standard Error	
99.9%	0.000136	0.000082	0.000001	73775

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE  
 (in mg/kg body wt/day)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000053	187,463	20.0	0.000185	54,011
80.0	0.000073	136,519	10.0	0.000234	42,731
70.0	0.000091	110,407	5.0	0.000281	35,633
60.0	0.000106	94,335	2.5	0.000327	30,535
50.0	0.000121	82,322	1.0	0.000386	25,927
40.0	0.000139	72,162	0.5	0.000453	22,073
30.0	0.000159	62,925	0.0	0.001559	6,413

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 1/ Margin of Safety = DPR NOEL ÷ Dietary Exposure

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 Chronic Exposure (EX1) Analysis for Fenoxaprop-Ethyl;      Section 3 Registration  
 RESIDUE FILE NAME: FNRICE1C (NFCS87/88 DATA)      ANALYSIS DATE: 03-02-1994  
 DPR NOEL (Chronic) = 0.9 mg/kg body-wt/day  
 EPA REFERENCE DOSE (RfD) = 0.0025 mg/kg body-wt/day  
 COMMENT 1: Registrant field residue data, 1/2 MDL for chronic nondetects  
 COMMENT 2: California rice labeled use  
 -----

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE <sup>1</sup> CODE
270	O	RICE-ROUGH (BROWN)	0.010000	1.00	1.00	REG-f
271	O	RICE-MILLED (WHITE)	0.010000	1.00	1.00	REG-f
408	O	RICE-BRAN	0.010000	1.00	1.00	REG-f

1/      REC-f =      Registrant supplied field residue data.

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 Chronic Exposure (EX1) Analysis for Fenoxaprop-Ethyl;                   Section 3 Registration  
 RESIDUE FILE NAME: FNRICE1C (NFCS87/88 DATA)                   ANALYSIS DATE: 03-02-1994  
 DPR NOEL (Chronic) = 0.9 mg/kg body-wt/day  
 EPA REFERENCE DOSE (RfD) = 0.0025 mg/kg body-wt/day  
 COMMENT 1: Registrant field residue data, 1/2 MDL for chronic nondetects  
 COMMENT 2: California rice labeled use  
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RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE <sup>1</sup> CODE
270	0	RICE-ROUGH (BROWN)	0.010000	1.00	1.00	REG-f
271	0	RICE-MILLED (WHITE)	0.010000	1.00	1.00	REG-f
408	0	RICE-BRAN	0.010000	1.00	1.00	REG-f

1/   REG-f =       Registrant supplied field residue data.

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 Chronic Exposure (EX1) Analysis for Fenoxaprop-Ethyl; Section 3 Registration  
 RESIDUE FILE NAME: FNRICE1C (NFCS87/88 DATA) ANALYSIS DATE: 03-02-1994  
 DPR NOEL = 0.9 mg/kg body-wt/day  
 EPA REFERENCE DOSE (RfD) = 0.0025 mg/kg body-wt/day  
 COMMENT 1: Registrant residue data, 1/2 MDL for chronic nondetects  
 COMMENT 2: California rice labeled use  
 -----

TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE		
	Mg/Kg Body Wt/Day	Margin of Safety <sup>1</sup>	Percent of RfD
U.S. POP - 48 STATES - ALL SEASONS	0.000002	463,201	0.1%
U.S. POPULATION - SPRING SEASON	0.000002	469,729	0.1%
U.S. POPULATION - SUMMER SEASON	0.000002	418,490	0.1%
U.S. POPULATION - AUTUMN SEASON	0.000002	528,327	0.1%
U.S. POPULATION - WINTER SEASON	0.000002	445,181	0.1%
NORTHEAST REGION	0.000002	513,860	0.1%
NORTH CENTRAL REGION	0.000002	552,100	0.1%
SOUTHERN REGION	0.000002	402,328	0.1%
WESTERN REGION	0.000002	445,322	0.1%
HISPANICS	0.000005	193,190	0.2%
NON-HISPANIC WHITES	0.000001	675,270	0.1%
NON-HISPANIC BLACKS	0.000003	261,939	0.1%
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.000008	107,732	0.3%
NURSING INFANTS (<1 YEAR OLD)	0.000003	314,435	0.1%
NON-NURSING INFANTS (<1 YEAR OLD)	0.000012	76,877	0.5%
FEMALES (13+/PREGNANT/NOT NURSING)	0.000001	>1,000,000	0.0%
FEMALES (13+/NURSING)	0.000003	320,541	0.1%
CHILDREN (1-6 YEARS)	0.000003	262,088	0.1%
CHILDREN (7-12 YEARS)	0.000003	312,120	0.1%
MALES (13-19 YEARS)	0.000002	450,859	0.1%
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.000002	531,419	0.1%
MALES (20+ YEARS)	0.000002	564,695	0.1%
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.000001	647,920	0.1%

<sup>1</sup>/ Margin of Safety = DPR NOEL ÷ Dietary Exposure Dosage

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 Chronic Exposure (EX1) Analysis for Fenoxaprop-Ethyl; Section 3 Registration  
 RESIDUE FILE NAME: FNALL1CH (NFCS87/88 DATA) ANALYSIS DATE: 03-02-1994  
 DPR NOEL (Chronic) = 0.9 mg/kg body-wt/day  
 EPA REFERENCE DOSE (Rfd) = 0.0025 mg/kg body-wt/day  
 COMMENT 1: Registrant field residue data, 1/2 MDL for chronic nondetects  
 COMMENT 2: California and federal labeled uses  
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RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE <sup>1</sup> CODE
239	A	PEANUTS-WHOLE	0.025000	1.00	1.00	REG
255	G	SOYBEANS-SPROUTED SEEDS	0.025000	0.33	1.00	REG
265	O	BARLEY	0.025000	1.00	1.00	REG
270	O	RICE-ROUGH (BROWN)	0.010000	1.00	1.00	REG-f
271	O	RICE-MILLED (WHITE)	0.010000	1.00	1.00	REG-f
276	O	WHEAT-ROUGH	0.025000	1.00	1.00	REG
277	O	WHEAT-GERM	0.025000	1.00	1.00	REG
278	O	WHEAT-BRAN	0.025000	1.00	1.00	REG
279	O	WHEAT-FLOUR	0.025000	1.00	1.00	REG
290	A	COTTONSEED-OIL	0.025000	1.00	1.00	REG
291	A	COTTONSEED-MEAL	0.025000	1.00	1.00	REG
293	A	PEANUTS-OIL	0.025000	1.00	1.00	REG
297	G	SOYBEANS-OIL	0.025000	1.00	1.00	REG
303	G	SOYBEANS-UNSPECIFIED	0.025000	1.00	1.00	REG
304	G	SOYBEANS-MATURE SEEDS DRY	0.025000	1.00	1.00	REG
305	G	SOYBEANS-FLOUR (FULL FAT)	0.025000	1.00	1.00	REG
306	G	SOYBEANS-FLOUR (LOW FAT)	0.025000	1.00	1.00	REG
307	G	SOYBEANS-FLOUR (DEFATTED)	0.025000	1.00	1.00	REG
318	X	MILK-NONFAT SOLIDS	0.005000	1.00	1.00	REG
319	X	MILK-FAT SOLIDS	0.005000	1.00	1.00	REG
320	X	MILK SUGAR (LACTOSE)	0.005000	1.00	1.00	REG
321	U	BEEF-MEAT BYPRODUCTS	0.005000	1.00	1.00	REG-m
323	U	BEEF-DRIED	0.005000	1.92	1.00	REG-m
324	U	BEEF(BONELESS)-FAT	0.005000	1.00	1.00	REG-m
327	U	BEEF(BONELESS)-LEAN (FAT/FREE)	0.005000	1.00	1.00	REG-m
328	U	GOAT-MEAT BYPRODUCTS	0.025000	1.00	1.00	REG
330	U	GOAT(BONELESS)-FAT	0.025000	1.00	1.00	REG
333	U	GOAT(BONELESS)-LEAN (FAT/FREE)	0.025000	1.00	1.00	REG
334	U	HORSE	0.025000	1.00	1.00	REG
336	U	SHEEP-MEAT BYPRODUCTS	0.025000	1.00	1.00	REG
338	U	SHEEP(BONELESS)-FAT	0.025000	1.00	1.00	REG
341	U	SHEEP(BONELESS)-LEAN (FAT FREE)	0.025000	1.00	1.00	REG
342	U	PORK-MEAT BYPRODUCTS	0.025000	1.00	1.00	REG
344	U	PORK(BONELESS)-FAT	0.025000	1.00	1.00	REG
347	U	PORK(BONELESS)-LEAN (FAT FREE)	0.025000	1.00	1.00	REG
398	X	MILK-BASED WATER	0.005000	1.00	1.00	REG
403	A	PEANUT-BUTTER	0.025000	1.89	1.00	REG

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 Chronic Exposure (EX1) Analysis for Fenoxaprop-Ethyl;      Section 3 Registration  
 RESIDUE FILE NAME: FNALL1CH (NFCS87/88 DATA)      ANALYSIS DATE: 03-02-1994  
 DPR NOEL (Chronic) = 0.9 mg/kg body-wt/day  
 EPA REFERENCE DOSE (RfD) = 0.0025 mg/kg body-wt/day  
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RESIDUE FILE LISTING (continued)

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ. #1	FCTRS #2	SOURCE CODE
408	O	RICE-BRAN	0.010000	1.00	1.00	REG-f
424	U	VEAL-(BONELESS)-FAT	0.005000	1.00	1.00	REG-m
425	U	VEAL-(BONELESS)-LEAN (FAT FREE)	0.005000	1.00	1.00	REG-m
429	U	VEAL-DRIED	0.005000	1.92	1.00	REG-m
430	U	VEAL-MEAT BYPRODUCTS	0.005000	1.00	1.00	REG-m
437	O	WHEAT-GERM OIL	0.025000	1.00	1.00	REG
940	A	PEANUTS HULLED	0.025000	1.00	1.00	REG

- 1/    REG -    Registrant supplied data.  
       REG-f =    Registrant supplied field residue data.  
       REG-m =    Registrant supplied metabolism and dietary data.

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Chronic Exposure (EX1) Analysis for Fenoxaprop-Ethyl;      Section 3 Registration  
RESIDUE FILE NAME: FNALL1CH (NFCS87/88 DATA)      ANALYSIS DATE: 03-02-1994  
DPR NOEL = 0.9 mg/kg body-wt/day  
EPA REFERENCE DOSE (RfD) = 0.0025 mg/kg body-wt/day  
COMMENT 1: Registrant supplied data, 1/2 MDL for chronic nondetects  
COMMENT 2: California and federal label uses  
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TOTAL EXPOSURE BY POPULATION SUBGROUP

POPULATION SUBGROUP	TOTAL EXPOSURE		
	Mg/Kg Body Wt/Day	Margin of Safety <sup>1</sup>	Percent of RfD
U.S. POP - 48 STATES - ALL SEASONS	0.000102	8,857	4.1%
U.S. POPULATION - SPRING SEASON	0.000099	9,063	4.0%
U.S. POPULATION - SUMMER SEASON	0.000100	8,964	4.0%
U.S. POPULATION - AUTUMN SEASON	0.000101	8,870	4.1%
U.S. POPULATION - WINTER SEASON	0.000106	8,514	4.2%
NORTHEAST REGION	0.000096	9,394	3.8%
NORTH CENTRAL REGION	0.000106	8,489	4.2%
SOUTHERN REGION	0.000101	8,928	4.0%
WESTERN REGION	0.000104	8,681	4.1%
HISPANICS	0.000091	9,894	3.6%
NON-HISPANIC WHITES	0.000101	8,876	4.1%
NON-HISPANIC BLACKS	0.000101	8,932	4.0%
NON-HISPANIC OTHER THAN BLACK OR WHITE	0.000124	7,279	4.9%
NURSING INFANTS (<1 YEAR OLD)	0.000038	23,665	1.5%
NON-NURSING INFANTS (<1 YEAR OLD)	0.000203	4,442	8.1%
FEMALES (13+/PREGNANT/NOT NURSING)	0.000075	12,066	3.0%
FEMALES (13+/NURSING)	0.000082	11,011	3.3%
CHILDREN (1-6 YEARS)	0.000269	3,351	10.7%
CHILDREN (7-12 YEARS)	0.000172	5,225	6.9%
MALES (13-19 YEARS)	0.000112	8,064	4.5%
FEMALES (13-19 YRS/NOT PREG. OR NURSING)	0.000088	10,267	3.5%
MALES (20+ YEARS)	0.000076	11,783	3.1%
FEMALES (20+ YEARS/NOT PREG. OR NURSING)	0.000064	13,978	2.6%

<sup>1</sup>/ Margin of Safety = DPR NOEL ÷ Dietary Exposure Dosage

**EXPOSURE ASSESSMENT FOR  
FENOXAPROP-ETHYL**

VOLUME II  
EXPOSURE ASSESSMENT DOCUMENT

HS-1695

(4-12-94)

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

# ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN FENOXAPROP-ETHYL

BY

Rhoda Wang, Staff Toxicologist

David Haskell, Associate Environmental Research Scientist

## EXECUTIVE SUMMARY

Fenoxaprop-ethyl is currently under review for possible registration in California as a selective post-emergent rice herbicide. Anomalies in fetal rats and liver toxicity in adult laboratory animals dosed with this chemical prompted the risk assessment for fenoxaprop-ethyl. Exposure to fenoxaprop-ethyl for workers mixing, loading, and applying (including cleanup) Whip® 1EC Herbicide with ground boom equipment to soybeans ranged from 0.42-27.2 mg per workday. Occupational exposure to workers involved in the aerial application of fenoxaprop-ethyl to rice experienced an estimated 2.32-18.80 mg of exposure per workday. Absorption data from a human study is not available. Seventy-three percent of a dermal dose of 2.3  $\mu\text{g}/\text{cm}^2$  in rats was considered absorbed after a 10 hour exposure period. The estimated absorbed daily dosage for workers applying fenoxaprop-ethyl with ground equipment was 1- 22  $\mu\text{g}/\text{kg}$  of body weight and 2.9-52  $\mu\text{g}/\text{kg}$  of body weight for workers making aerial applications.

Two major metabolites, benzoxazol mercapturic acid and a hydroxy-phenoxy propionic acid were detected in the urine of rats with a  $^{14}\text{C}$  labeling technique. An extensive discussion, both pro and con, is provided in this document with respect to the usefulness and limitations of applying biomarkers for estimating the absorbed dose for this herbicide in humans.

## PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of a pesticide can determine its rate of absorption by the skin and how extensive it is metabolized by the human body.

Chemical Family	:	aryloxy-phenoxy-propionate derivatives
Chemical Name	:	(±) - ethyl 2-[4-[(6-chloro-2-benzoxazolyl)oxy]-phenoxy]propanoate
Common Name	:	fenoxaprop-ethyl
Trade Names	:	Whip <sup>®</sup> , Whip 360 <sup>®</sup> , Acclaim <sup>®</sup> , Depon <sup>®</sup> , Excel <sup>®</sup> , Furore <sup>®</sup> , Option <sup>®</sup> , Option II <sup>®</sup> , Bugle <sup>®</sup> , Cheyenne TP <sup>®</sup> , Horizon <sup>®</sup> , Tiller <sup>®</sup>
CAS Number	:	66441-23-4
Empirical Formula	:	C <sub>18</sub> H <sub>16</sub> ClNO <sub>5</sub>
Molecular Weight	:	361.8 daltons
Melting Point	:	80-85°C
Boiling Point	:	>300°C @ 760 mm Hg
Stability	:	Half-Life- aqueous media (pH 9) @ 20°C, 2.4 days.
Solubility @ 25°C	:	water : 0.8 - 0.9 mg/kg toluene : >300 g/kg acetone : >500 g/kg ethyl acetate : >200 g/kg cyclohexane, ethanol, octanol : 10 g/kg.
Appearance	:	Colorless solid
Vapor Pressure	:	19 nPa @ 20°C; 3.2 x 10 <sup>-8</sup> mm Hg @ 25°C.
K <sub>ow</sub>	:	19,200 (log K <sub>ow</sub> = 4.28)
pH	:	5.4 ± 1 ( 1% suspension, distilled water)

## REGULATORY HISTORY INCLUDING EPA STATUS

Fenoxaprop-ethyl containing products are currently registered conditionally by the US EPA in accordance with FIFRA section 3(C) (7) (C). Fenoxaprop-ethyl is not registered for any use in California. However, Whip<sup>®</sup>, a rice herbicide, is currently under review as the first section three registration of this active ingredient in California.

## TECHNICAL AND PRODUCT FORMULATIONS

Whip<sup>®</sup> IEC Herbicide is an emulsifiable concentrate formulation of fenoxaprop-ethyl that contains 1 pound of active ingredient (a.i.) per gallon, i.e. 12.5% fenoxaprop-ethyl and 87.5% inerts.

## USAGE

The supplemental label for the proposed registration of Whip<sup>®</sup> IEC Herbicide in California permits the post-emergent control of annual grasses in rice. This product can be applied by ground or air equipment but may not be applied with irrigation water. The maximum application rate for rice is 3.2 ounces of active ingredient (a.i.) per acre with a maximum of 4.8 ounces of a.i. per growing season. The proposed label requires applications to be made with a minimum of 10 gallons of water per acre to obtain thorough coverage. Whip<sup>®</sup> IEC Herbicide is registered for use in other states for selective post-emergent control of annual and perennial grasses in rice, wheat, soybeans, cotton, peanuts and acreage conservation reserve (set-aside).

## LABEL PRECAUTIONS/PERSONAL PROTECTIVE CLOTHING

The Whip<sup>®</sup> IEC Herbicide label carries the signal word, "WARNING", with the following precautionary statements:

"May cause substantial but temporary eye injury. Do not get in eyes.  
Avoid contact with skin or clothing. Harmful if swallowed, absorbed through skin or inhaled. Do not take internally. Avoid inhalation of vapor or spray mist. Remove contaminated clothing and wash before reuse."

The precautionary statements indicate the category II toxicity classification is due to the temporary eye injury that is reversible within 7 days. The statements for oral, inhalation and dermal exposure indicate these routes have a toxicity category III classification.

The latest proposed label for Whip<sup>®</sup> requires the following protective clothing to be worn: (a) pilots - long-sleeved shirt and long pants, shoes and socks, chemical resistant gloves and protective eyewear; (b) mixer/loaders - long-sleeved shirt and long pants underneath a chemical resistant suit, shoes and socks, chemical resistant gloves, and protective eyewear; (c) flaggers - long-sleeved shirt and long pants, shoes and socks, chemical resistant gloves and protective eyewear.

## WORKER ILLNESSES/INJURIES

Since this product is not registered in California, there are no available data regarding exposure-related illness reported in California.

## DERMAL IRRITATION/SENSITIZATION

Fenoxaprop-ethyl has a low acute mammalian toxicity. It is classified as a category II eye irritant. The label requires eye protection and impermeable rubber gloves to be worn by workers when handling this product. A dermal sensitization test conducted with guinea pigs did not indicate this product is an animal dermal sensitizer (Jung and Weigand, 1982).

## DERMAL ABSORPTION OF FENOXAPROP-ETHYL

Labeled  $^{14}\text{C}$ -fenoxaprop-ethyl (98% radiopurity, chlorphenyl  $^{14}\text{C}$  labeled) was prepared as a homogeneous suspension and applied dermally to four groups (20 animals per group) of female rats (Laveglia *et al.*, 1986). Each dose was applied within a rubber ring encompassing  $10.8\text{ cm}^2$  which was cemented to a shaved area of skin. After application of the dose, a cover of filter paper was cemented in place on the rubber ring to cover the application site. The dermal dose applied to each group was 2.3, 23, 231, and  $2315\ \mu\text{g}/\text{cm}^2$ , respectively. The lower doses were administered as a known amount of the test substance mixed with the blank EC formulation and then diluted with water. The highest dose, however, was administered without the water dilution. The animals were individually placed in metabolic cages for urine and fecal collection and sacrificed after 0.5, 1, 2, 4, or 10 hours of exposure. Another group of rats (8 animals) was exposed to the highest dose level for 10 hours before removal of the dose by washing. These rats were kept an additional 24 or 72 hours and their excreta collected until sacrifice.

The skin washing after the 10-hour exposure period removed an average 24% of the dose in all dose groups (range 19-60%). Although radioactivity appeared in the urine as early as 0.5 hour after the dermal exposure to fenoxaprop-ethyl began, the amount of radioactivity in the excreta did not increase substantially over time for those groups sacrificed at 0.5-10 hours. After 10 hours of exposure, less than 2% of the dose was detected in the excreta of these treatment groups. Rats sacrificed 24 hours after washing the  $2315\ \mu\text{g}/\text{cm}^2$  dose excreted approximately 1.2% of the dose. However, for those rats held 72 hours after washing the  $2315\ \mu\text{g}/\text{cm}^2$ , 12% of the dose was detected as fenoxaprop-ethyl equivalents in the excreta. The significant increase in the percentage (5.9%) of the dose excreted in the feces, 72 hours after washing the dose, suggests that either prolonged dermal absorption or enterohepatic circulation was taking place.

The amount of fenoxaprop-ethyl absorbed from a dermal application was defined as the sum of the fenoxaprop-ethyl equivalents present in various tissues (blood, internal organs), the excreta, the carcass and the bound skin residues present at the application site. The equivalents detected at the application site accounted for more than 90% of the material considered absorbed for most groups of rats. Data from the observations of rats sacrificed at 24 and 72 hours after the dose was washed off, indicate the bound skin residues continue to migrate into the body and therefore must be considered bioavailable. The percent of the dose absorbed (in parenthesis) at various dose levels 10 hours after dosing the rats was found to be:  $2.3\ \mu\text{g}/\text{cm}^2$  (73%);  $23\ \mu\text{g}/\text{cm}^2$  (62%);  $231\ \mu\text{g}/\text{cm}^2$  (43%); and  $2315\ \mu\text{g}/\text{cm}^2$  (70%) (Table 1).

This phenomenon is not normal. The lowest and highest dose (a span of one thousand fold) were absorbed at almost the same rate (73 and 70%). It is usually observed in dermal absorption studies that the percent of absorbed dose decreases as the amount of dose increases when the exposed skin area is kept constant. The study authors hypothesized this phenomena was due to the disparity in the adjuvants used to dissolve the test material. The highest dose was administered with an organic solvent-based formulation which tends to accelerate dermal penetration as compared to a water-based emulsion applied to the rest of the treatment groups. The other plausible explanation, though unlikely as a major contributory factor, is the potential disparity in the amount of radioactivity removed through the washing procedure.

Seventy-three percent of the low dose (2.3  $\mu\text{g}/\text{cm}^2$ ) was considered absorbed and bioavailable after a 10 hour exposure period. This rate included the percentage of a dermal dose that was bound to the application skin site. Without additional excretion data that could identify the fate of the bound-skin residues over time and the observation that fenoxaprop-ethyl equivalents continue to be excreted after 24 hours, the assumption has to be made that the bound-skin residues will ultimately be bioavailable. In the absence of human absorption data, this 73% absorption rate will be used as the human dermal absorption rate. It was derived from the lowest dosage rate which is closest to the estimated rate of occupational exposure.

An asymptotic extrapolation of the excreted dose via an iterative process over time was attempted with the excretion data to determine the ultimate fate of the bound skin residues (Thongsinthusak, 1994). This procedure allows the direct computation of the absorbed dose from the excreted dose, and thus, the skin-bound residues can be disregarded. However, this extrapolation technique is not applicable to this study because of the very high dose administered to the test animals and the excretion of the fenoxaprop-ethyl metabolites was not complete at 72 hours.

It is known that the dermal absorption capacity of rats for many chemicals far exceeds that of man. It has been observed that rats can dermally absorb pesticides at rates 4-16 fold greater than humans exposed to the same pesticides (Wester and Maibach, 1993; Wester *et al.*, 1989; Shah *et al.*, 1981). The pharmacokinetics of chemical absorption and disposition processes dictate the target organ concentration which in turn determines whether a threshold adverse effect, i.e. hepatotoxicity will or will not occur. For a chemical that is released very slowly through the dermal route of exposure and assuming a non-cancer endpoint, the overt toxic effect may not be manifested because the threshold dose cannot be reached at any point during or after the exposure. Since the absorption from skin-bound fenoxaprop-ethyl is a very slow process, there is a continuous disposition of fenoxaprop-ethyl equivalents (tissue distribution, biotransformation and excretion). However, the kinetics of the dose distribution to the tissues and organs after the exposure is most critical. At 10 hours post exposure, the amount of radioactivity (expressed as nanograms per gram of wet tissue), was the highest in liver, kidneys and blood. The concentration patterns and the distribution of the absorbed dose to the target organs may be compared to the adverse effect seen in various studies.

## METABOLISM OF FENOXAPROP-ETHYL

There are eight reports on fenoxaprop-ethyl metabolism in mammals on record. These studies were conducted at Hoechst Agricultural Laboratory in Germany. Five of the eight reports were reviewed to identify potential urinary metabolites (FIGURE 1) for possible worker exposure biomonitoring and to ascertain the feasibility of applying the established analytical methods. The laboratory reports issued by the registrant described in great length the analytical techniques used in the isolation and identification of metabolites.

The first study conducted by Dorn *et al.* (1982) includes orally administered  $^{14}\text{C}$  fenoxaprop-ethyl to female rats at 40 mg/kg and monitoring urinary and fecal excretion for metabolites at 24-hour intervals. The rates of excretion of the radioactivity in the urine and feces were measured with a

liquid scintillation counter. The metabolites were separated and purified through thin-layer chromatography (TLC) and high pressure liquid chromatography (HPLC). GC-MS methodology was used to identify the structure of the parent/metabolites by reference to synthesized standards. The amount of radioactivity excreted via urine and feces was high; over 75% (combined) of the dose excreted by 48 hours and over 95% by 168 hours after dosing.

The second study (Dorn *et al.*, 1985) includes oral dosing of both male and female rats at a single dose (2 mg-10 mg/kg), or multiple dose (2 mg/kg) with <sup>14</sup>C labeled fenoxaprop-ethyl (98% radiochemically pure and labeled at chlorophenyl U <sup>14</sup>C position). In the multiple dosing regimen, 14 daily doses of unlabeled fenoxaprop-ethyl were given to rats followed with a pulse of <sup>14</sup>C labeled fenoxaprop-ethyl on the 15th day. The objective of this study was to discern sex and dose effects, if any, on the metabolism of fenoxaprop-ethyl.

In the third study (Burkle *et al.*, 1985), dioxyphenyl-<sup>14</sup>C ring-labeled fenoxaprop-ethyl (96% radiochemically pure) was applied orally to rats at 2 and 10 mg/kg dose levels. This study was designed to investigate metabolic pathways using various ring-labeling techniques. A fourth study (Dorn *et al.*, 1984) was a comparative investigation on the metabolism of orally dosed <sup>14</sup>C fenoxaprop-ethyl in various animals. This research included a group of pregnant rats that received 50 mg/kg of fenoxaprop-ethyl between day 7 and 16 of organogenesis. Also included were pregnant rabbits (50 mg/kg) and one pregnant Cynomolgus monkey (10 mg/kg). The final study (Kellner and Eckert, 1984a) entailed the oral dosing of rats for 14 days with un-labeled fenoxaprop-ethyl at 2 mg/kg body weight followed by a single dose of 2 mg/kg of body weight of <sup>14</sup>C labeled fenoxaprop-ethyl. The rate of excretion of the dose in the urine and feces and the deposition of the dose in the organs and tissues was determined.

At a dose level of 2 mg/kg administered orally to male and female rats, the percent of the dose excreted as <sup>14</sup>C equivalents of fenoxaprop-ethyl after 96 hours was 42.1-53.9% in the urine and 33.8-40.4% in the feces (Dorn *et al.*, 1985). The postulated metabolic pathway is shown in Figure 1. The mercapturic acid is a major metabolite and amounts to approximately 14.6-26% of a given dose in rats (Dorn *et al.*, 1985). The other major metabolite, a hydroxy-phenoxy propionic acid can be detected in the urine of rats (27.5-49.6%) when the dioxyphenyl ring is labeled with <sup>14</sup>C (Burkle *et al.*, 1985). Five minor metabolites including the free acid, 2-(4-(6-chloro-2-benzoxazolylloxy)-phenoxy)-propionic acid, the hydroxy isomers (4 and 5-6-chloro-2, 3-dihydrobenzoxazol-2-one), the benzoxazol (6-chloro-2, 3-dihydro-benzoxazol-2-one) and a thio compound (6-chloro-2,3-dihydrobenzoxazol-2-thione) were identified in small quantities, each representing 2-7% of a given dose (Dorn *et al.*, 1985).

The elimination of fenoxaprop-ethyl and/or its radiolabeled metabolites in the urine and feces of rats was biphasic, regardless of the sex of the animals (Kellner and Eckert, 1984a). The biological half-lives for the rapid phase I ranged from 8.5 to 12.5 hours (urine and feces). For the slower phase II, half-lives were 41-73 hours for urine and 27-34 hours for feces.

Approximately 66% of the total radioactivity was extractable from the feces with the rest remaining uncharacterized. The recovery of the dose from the feces which represented

unchanged fenoxaprop-ethyl was estimated at 12%. The major metabolite (8-22%) was identified as the free acid. Other moieties were unidentifiable.

With respect to the effect of sex and varying treatment regimen on metabolism, there were no qualitative differences discerned in the excreted metabolites. However, there may be quantitative differences with respect to certain chemical species of metabolites being biotransformed and excreted. Notably, when female rats were given a single oral dose of 10 mg/kg of fenoxaprop-ethyl, or a repeated low dose of 2 mg/kg of fenoxaprop-ethyl, the excretion of the free acid was increased with a corresponding decrease in the mercapturic acid (Dorn *et al.*, 1985). The metabolites identified in the urine and feces of pregnant rats receiving fenoxaprop-ethyl throughout organogenesis did not differ qualitatively from those observed in other groups of rats (Dorn *et al.*, 1984). Since the dose administered was high (50 mg/kg) the amount of free acid was increased (21%), with a corresponding decrease of the mercapturic acid metabolite (10%).

The residue concentrations of fenoxaprop-ethyl and its metabolites in the tissues and organs were measured seven days after oral dosing at 2 and 10 mg/kg (Kellner and Eckert, 1982, 1984a, 1984b). The total residues at day seven ranged from 2.2 to 5.1% of the dose, irrespective of the dosages given which indicates a long tissue half-life. The residual metabolites were found in adipose tissues and excretory organs such as kidneys.

In the multiple species of pregnant animals studied, a similar pattern of metabolism was observed in all animals (Dorn *et al.*, 1984). Quantitative differences exist with respect to biotransformation rate and tissue deposition of the three species. Tissue deposition pattern was observed to be in the following order: rat>rabbit>monkey.

Theoretically, since the two major urinary metabolites, namely the benzoxazol mercapturic acid and the hydroxyphenoxy propionic acid may constitute over 50% of an administered dose, potentially, they may be used as biological markers for urinary monitoring. Because of the slow excretion of metabolites (slow phase) and the possible interferences with endogenous polar metabolites, the isolation and identification of these metabolites is perceived to be difficult. Kinetic studies on the urinary elimination half-lives of fenoxaprop-ethyl in female and male rats indicate they span a range from 41 to 73 hours. This suggests the biomonitoring period should be a minimum of four days post exposure to maximize the total recovery of metabolites from urine.

## WORKER EXPOSURE

The proposed registration for Whip<sup>®</sup>1 EC Herbicide on rice is to control grassy weeds early in the growing season. Applications can be made when the rice has 5-7 leaves (25 days after planting) until panicle initiation (60 days after planting). Since fenoxaprop-ethyl acts primarily as a contact herbicide, the rice fields need to be drained or at least the water level lowered to expose the target foliage. The proposed label allows applications to be made by ground and aerial equipment. Most of the treatments will be made by aircraft due to the ease of application and the narrow use season (mid-May to mid-June) permitted by the label. However, ground equipment may be used to make spot treatments along roads and canal banks and to treat rice fields located

next to sensitive crops (corn and sorghum) and environmental areas where aerial applications may cause drift problems.

#### GROUND APPLICATION

A worker exposure study was conducted in by Orius Associates Inc. (1985) on behalf of the American Hoechst Corporation. Three workers at the American Hoechst Corporation field research station in Leland, Mississippi served as volunteers to apply fenoxaprop-ethyl 1.0 EC herbicide (1.0 lb fenoxaprop-ethyl/gal) with a ground boom tractor to soybeans for 1 day each. Each worker was monitored for exposure with dermal dosimeters and personal air pumps, while performing the tasks of mixing/loading, application and cleanup of the tractor. The herbicide (EPA Registration No. 8340-EUP-7) was supplied in 5-L metal containers with integrated pouring spouts. Fenoxaprop-ethyl was applied at the maximum label rate of 0.20 lb a.i./acre with 30 gallons of water. No adjuvants or other pesticides were used. During spraying, a record was kept of the wind speed, wind direction, temperature, relative humidity, and cloud cover.

The typical work day consisted of filling the tanks with water at the station, measuring and loading the herbicide, and spraying until empty. Tanks were refilled with water from a nurse tank at the field and the tasks were repeated. For maximum exposure, all workers drove tractors equipped with only a roll bar cage and roof. The three workers applied 6-8 tank loads each for the workday that was monitored. They handled an average of 9.8 lbs of fenoxaprop-ethyl per day and treated an average of 49 acres. All the sprayers were cleaned after the last application of the day. The duration of the workday (mix/load, apply and clean) ranged from 8-11 hours.

Exposure to the body was estimated by way of a multilayer dosimeter which allowed the estimation of potential exposure, as well as the determination of the efficacy of various layers of clothing in preventing dermal exposure. These dosimeters consisted of a cellulose glassine backing covered with one to three layers of 100% cotton or poly-ester/cotton material to represent various regimes of protective clothing. These layers were then encased in a waterproof vinyl plastic "badge holder" with a 40-cm<sup>2</sup> open window to allow exposure. The dosimeters (total of 11) were taped to the work clothing or Tyvek<sup>®</sup> coveralls worn by the workers at the following locations; head, chest and back, both shoulders upper arms, both forearms, left and right thighs and on both lower leg/ankles.

Exposure to the hands was measured as the total residues present in the hand rinses. Each hand was vigorously triple-rinsed in 750-ml of 10% (v/v) isopropyl alcohol in distilled water. For the first replication of the mixing/loading and spraying work tasks, each worker wore impermeable gloves; neoprene by Worker A on Day 1, or polyvinyl chloride (PVC) type by Workers B and C on Days 2 and 3. The outside of each glove was rinsed and each hand was rinsed for each task. The subsequent replications of the work tasks were conducted with the workers working bare-handed.

Inhalation exposure was measured by sampling the air in each workers' breathing zone with two MSA Fixt-Flo<sup>®</sup> personal air pumps. Charcoal tube traps were used at air flow rates of 0.5 L/min for one pump and 1.0 L/min, the maximum recommended by MSA, for the other pump. Different sampling strategies were used to assess the amount of dermal and inhalation exposure. Sampling

periods included a half day, full day, and the durations of the tasks of mixing/loading, spraying, and cleaning-up. Exposure was partitioned into dermal exposure for each part of the body and inhalation. Exposure was estimated for workers wearing only long pants and a long-sleeved shirt with a T-shirt. In addition to this work clothing, the proposed Whip<sup>®</sup> 1EC Herbicide label requires workers mixing this product to wear impermeable rubber gloves and goggles or a face shield.

Residues of fenoxaprop-ethyl were extracted from the monitoring media with toluene and measured by gas chromatography. All residue values were adjusted for recoveries from samples fortified in the field. In order to pool results for statistical purposes and to compare the exposures of different workers, all exposures were standardized to a rate of  $\mu\text{g a.i./person/lb a.i.}$  handled in the monitoring period.

The occupational exposure for the three workers is summarized in Table 2. Each value represents the  $\mu\text{g}$  of fenoxaprop-ethyl exposure per pound a.i. of fenoxaprop-ethyl applied for one full workday for each operator. The greatest exposures occurred to the unprotected hands which accounted for approximately 97% of the exposure for workers, mixing, loading and applying fenoxaprop-ethyl. This high percentage is due in part to operator C who was exposed while repairing a broken line on the belly tank of the spray tractor. The Average Daily Exposure (dermal and inhalation) for the three operators was 10 mg/workday. By comparing the hand exposures with or without gloves, it was observed that wearing neoprene or PVC gloves reduced exposure by 94%. When gloves were worn, exposure of the hands still contributed significantly to total exposure. Based on task-related samples, exposure was greatest during mixing/loading, followed by spraying and clean-up.

#### AERIAL APPLICATION

The majority of the applications for the proposed Whip<sup>®</sup> 1EC Herbicide registration on rice will be made by aircraft. The use of the ground application exposure study for fenoxaprop-ethyl as a surrogate for aerial application is not suitable. During aerial application, the work tasks are separate with the pilot as the applicator and another worker as the mixer/loader. Also, aircraft are capable of treating much larger acreages and the mixer/loader will handle greater amounts of active ingredient. An exposure study of the aerial application of Londax<sup>®</sup> herbicide (bensulfuron-methyl) with a dry flowable formulation was used to estimate the exposure to workers when fenoxaprop-ethyl is applied by air because of similarities in use practices and application rate.

Two studies were conducted concurrently by Jensen and Merricks (1991) with aerial applicators located in the Sacramento Valley. The workers of two companies were monitored for dermal and inhalation exposure during the application of bensulfuron methyl at three different sites. The spray crews, consisting of a mixer/loader, pilot and flagger applied five-ten (average eight) loads of bensulfuron-methyl per workday treating approximately 60 acres per load. Bensulfuron-methyl was applied at the rate of one ounce of active ingredient (a.i.) per acre with five gallons of water. Some applications were made at a higher dilution rate to enhance coverage. A total of 80 tank loads were applied during the ten workdays. The average exposure time per workday for the application personnel was: pilots-3.2 hours, mixer/loaders-3.2 and flaggers-3.0 hours. At the conclusion of the bensulfuron methyl applications, the pilot for each aircraft was monitored for

dermal and inhalation exposure (approximately 2 hours) while performing the extensive cleaning activities required for the removal of bensulfuron-methyl residues from the aircraft.

Dermal exposure for the workers was monitored with a long sleeved T-shirt (cotton) and long underwear (cotton blend) worn underneath their work clothing (coveralls, shoes and socks). In addition the mixer/loaders wore rubber gloves and the pilots wore cotton or leather gloves. Exposure to the hands was monitored with a hand wash made with 500 ml of an aqueous detergent solution in a gallon Ziploc<sup>®</sup> plastic bag. The face and neck were wiped thoroughly with a cotton cloth saturated with a detergent solution. Inhalation exposure was monitored with a personal sampling pump attached to the worker. Air samples were collected by drawing air from the breathing zone at the rate of 2 liters /minute through two polyurethane foam filters. The pumps were operated only during the actual pesticide handling periods.

The results from analysis of the spiked/control samples indicate the analytical methodology was appropriate and the experimental values observed were reliable. The recoveries from the lab spiked sample matrices were greater than 90% over a range of fortification levels with the exception of the polyurethane foam plugs (76-97%) and one hand wash sample (89.9%). The mean rates of recovery from the matrix samples spiked in the field at the three sites were greater than 90% for all sample media with the exception of the T-shirts (89.4%). Residues were not detected on any of the control samples taken in the field. The results from the storage stability study indicate the bensulfuron residues were stable in the experimental matrices. Recovery of the lab spiked samples was greater than 95% after 90 days of frozen storage. The average recovery of bensulfuron from the spray tank samples was 83.6% for the minimum dilution rate of one ounce a.i. per five gallons of water.

Dermal exposure was expressed as the residues detected per cm<sup>2</sup> of skin surface area or in the hand wash solutions per pound of a.i. applied. If residues were not detected for a particular sample, then one-half the detection limit for the particular sample medium was used to derive an exposure value. The results were reported as the exposure (dermal and inhalation) to bensulfuron-methyl incurred per pound of a.i. applied multiplied by the total pounds of a.i. applied per workday (Table 3) to derive a total daily exposure.

The spray crews (mixer/loader, pilot and flagger) at the three sites did not work equivalent workdays. The amount of bensulfuron-methyl applied and exposure time per workday varied from site to site. The spray crews applied from 20.8-33.6 lbs of bensulfuron per day treating approximately 333-538 acres of rice. The appropriate method for expressing this variability is to normalize the exposure as ug of exposure per pound a.i. applied. Table 3 summarizes the inhalation and dermal exposure to the various body regions for mixer/loaders, pilots and flaggers involved in the application of bensulfuron-methyl. Each value represents the average exposure in µg per pound of a.i. handled from 3-4 replicates (workdays) at each site. The greatest dermal exposures occurred to the arms of the workers: mixer/loaders-41.9 µg/lb a.i., pilots-25.0 µg/lb a.i. and flaggers-32.7 µg/lb a.i.. Some workers rolled their coveralls up to their elbows while performing the work tasks, exposing the long-sleeved T-shirt dosimeters. This work practice may be due to the high temperatures (range 92-96° F) that occurred during part of the study. Exposure to the hands of all the workers was less: mixer/loaders-18.8 µg/lb a.i., pilot-11.5 µg/lb

a.i. and flaggers-10.7 µg/lb a.i.. Inhalation exposure was minimal for all work tasks with 30% of the samples with residues below the limit of detection. The work task of mixing/loading incurred the greatest inhalation exposure with a maximum of 4.7 µg of exposure experienced by one mixer/loader during one workday.

The average daily exposure (dermal and inhalation) to bensulfuron-methyl was: pilots-1.95 mg (range 0.50-2.76 mg), mixer/loaders-2.47 mg (range 0.94-3.62 mg) and flaggers-2.19 mg (range 0.30-3.93 mg). During the cleanup procedure, the pilots experienced an average of 1.1 mg of dermal exposure.

The average daily bensulfuron-methyl exposure for each of the work tasks listed in Table 3 was: pilot-66 µg, mixer/loader-85 µg and flagger-72 µg per pound of a.i. applied. In order to use these values for estimating the exposure to fenoxaprop-ethyl from aerial applications, some adjustments need to be made for the protective clothing worn in the Londax<sup>®</sup> study. The proposed Whip<sup>®</sup> label requires workers (pilots, mixer/loaders and flaggers) to wear work clothing (long-sleeved shirt and long pants, shoes and socks), chemical resistant gloves and protective eyewear.

Workers mixing and loading Whip<sup>®</sup> may also need to wear an apron and use a closed system. The EPA Worker Protection Standard will require pilots to wear chemical resistant gloves when entering or leaving an aircraft contaminated with pesticide residues. California regulations also require the pilot to wear chemical resistant gloves when adjusting, cleaning or repairing contaminated mix, load and application equipment. In the Whip<sup>®</sup> ground applicator study (Orius Associates Inc., 1985), it was observed that chemical resistant gloves reduced fenoxaprop-ethyl exposure to the hands by 94%. To derive the average daily exposure to fenoxaprop-ethyl for workers making ground applications in Table 5 when gloves are worn, the hand exposures observed in Table 2 study were multiplied by 0.06 to correct for the protection provided by wearing gloves.

Pilots are required by the proposed Whip<sup>®</sup> label to wear chemical resistant gloves. Pilots wore leather or cotton gloves in the bensulfuron-methyl exposure study and the protection provided by these materials is generally believed to be less than chemical resistant. As a result a correction needs to be made for the exposure to the hands of the pilots. This correction was made in Table 4 with exposure data from a study by Maddy *et al.* (1984) that observed the exposure to the hands of pilots not wearing gloves represented approximately 54.5% of the total exposure.

The label rate for Whip<sup>®</sup> 1EC Herbicide on rice is 2.4-3.2 oz. of a.i. per acre with a minimum of 10 gallons of water per acre. In the bensulfuron-methyl study, 333-538 acres of rice were treated per workday with a minimum of 5 gallons of water per acre. The higher minimum dilution rate for Whip<sup>®</sup> 1EC Herbicide can reduce the rice acreage by 33% that can be treated in a workday (Jones, 1993). This is due to the fact that fewer acres can be treated per load. By reducing the treated bensulfuron-methyl acreage by 33%, the fenoxaprop-ethyl handled during the Whip<sup>®</sup> 1EC Herbicide applications would range from 33-72 lbs of a.i. per workday. Exposures in Table 5 were calculated based on the maximum application rate. These estimates of lbs a.i. applied per workday in conjunction with the daily exposure rates from the bensulfuron methyl study were used to derive the daily exposures to fenoxaprop-ethyl in Table 4 for the pilots, mixer/loaders and

flaggers. These exposures are based on the maximum acres treated per day (360) and the maximum rate of fenoxaprop-ethyl applied (3.2 ozs a.i. per acre).

Tables 4 and 5 estimate the daily exposure and the seasonal average daily dosage for workers mixer/loading and applying fenoxaprop-ethyl and for workers flagging aerial applications, based on 8 hours of exposure per workday. These formulas were used to calculate the various levels of occupational exposure.

**Total Daily Exposure** (mg/person/8 hour-day) = directly estimated from dosimeters placed underneath the protective clothing and observed inhalation exposure.

**Absorbed Daily Dosage, ADD** ( $\mu\text{g}/\text{kg}/\text{day}$ ) = (Daily Dermal Exposure  $\times$  % dermal absorption) + (Inhalation Exposure  $\times$  % absorption)  $\times$  1,000  $\mu\text{g}/\text{mg}$   $\div$  weight (male 76 kg).

**Seasonal Average Daily Dosage, SADD** ( $\mu\text{g}/\text{kg}/\text{day}$ ) = ADD  $\times$  days exposed/number of days per use season.

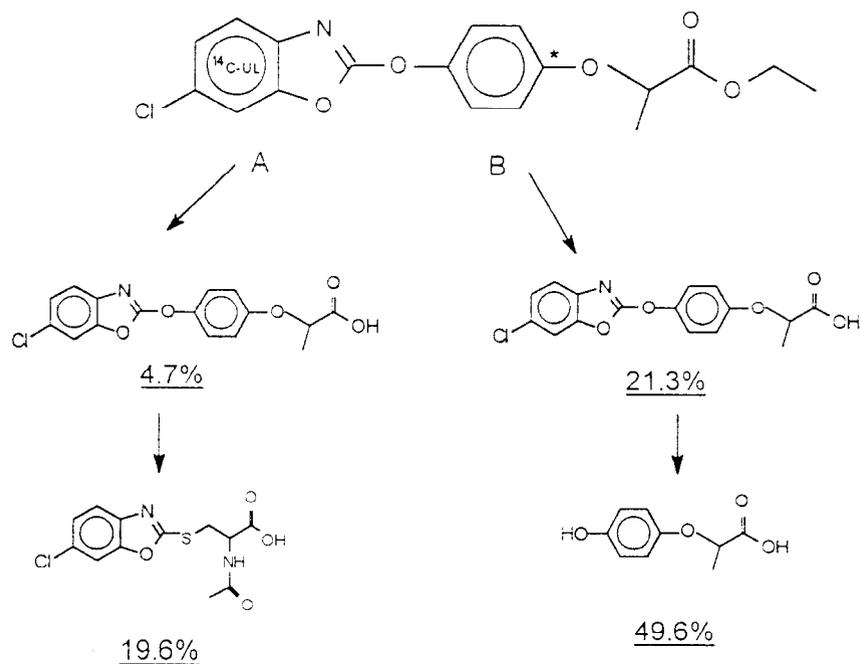
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FIGURE 1. The Pathway for Urinary Metabolites of  $^{14}\text{C}$  Fenoxaprop-Ethyl Labeled in the Chlorophenyl-U Position (A) and the Dioxyphenyl-1 Position (B)<sup>a,b</sup>.



a. Female rats were given a single oral dose of 2 mg/kg b.w. of  $^{14}\text{C}$  fenoxaprop-ethyl and the urinary excretion was collected for 96 hours. Rats dosed with the  $^{14}\text{C}$  label in the chlorophenyl-U position (Dorn *et al.*, 1985) had 54 % of the dose recovered in the urine. Rats dosed with the label in the dioxyphenyl-1 position (Burkle *et al.*, 1985) had 71% of the dose recovered in the urine.

b. The percentage values represent the percent of the dose that was excreted as the noted metabolite in urine. The parent material was not detectable in the urine.

**Table 1. The Average Percent of a Dermal Dose Absorbed by Rats After a Ten Hour Exposure to Radio-Labeled Fenoxaprop-Ethyl**

GROUP No.	APPLIED DERMAL DOSE (ug)	FENOXAPROP-ETHYL DETECTED				% OF DOSE ABSORBED
		TISSUES(a) (ug)	CARCASS (ug)	EXCRETA(b) (ug)	SKIN SITE(c) (ug)	
I.	21.9	0.77	1.19	0.34	13.9	73
II.	213	3.04	5.75	1.79	122	62
III.	1,894	10.7	23.0	10.0	771	43
IV.	23,658	150	94.4	49.3	16,482	70

Haskell, WH&S, 1993.

(a) Tissues are the blood, fat, kidney, liver, ovaries and uterus.

(b) Urine and feces.

(c) The skin at the application site and the skin adjacent to the rubber ring that protected the application site.

**Table 2. The Average Daily Exposure to Fenoxaprop-Ethyl For Mixer/Loaders and Applicators Making Ground Applications to Soybeans**

WORK TASK (worker #)	AVERAGE DAILY FENOXAPROP-ETHYL EXPOSURE (a,b) (ug of exposure/lb of a.i. applied)					LBS A.I. APPLIED PER WORKDAY	TOTAL DAILY EXPOSURE (c) (mg)
	foam filter	hand wash	face/neck	lower/upper body	total		
<b>Mix/Load/Apply and Clean</b>							
operator A	3.50	36.3	2.0	4.0	45.8	9.25	0.42
operator B	1.80	293	3.0	5.0	303	8.03	2.43
operator C*	1.20	2173	26.0	36.0	2236	12.05	27.2
AVERAGE	2.17	834	10.3	15.0	862	9.8	10.0

Haskell, WH&S, 1993

\*Operator C repaired a broken hose that connected the two belly tanks on the tractor.

(a) The source of the data from the study (Orius Associates Inc., 1985) are: respiration (foam filters)-Table 5, hand wash-Tables 8 and 9, face/neck-Tables 28, 32 and 36, and lower/upper body-Tables 28, 32 and 36.

(b) The exposure estimate when workers wore long pants, a long-sleeved shirt and no chemical resistant gloves.

(c) The TOTAL DAILY EXPOSURE (mg) was calculated as the total AVERAGE DAILY FENOXAPROP-ETHYL EXPOSURE (ug) per lb a.i. applied multiplied by the AVERAGE LBS A.I. APPLIED PER WORKDAY divided by 1000 (ug/mg).

The Whip 1EC Herbicide label requires operators mixing fenoxaprop-ethyl to wear chemical resistant gloves.

The exposure mitigation provided by the gloves can be estimated by multiplying the value in Table 8 of the study (Orius Associates Inc., 1985) for exposure to both hands (ug a.i./lb a.i.) of each worker by 94% (% protection observed in the study for gloves). This value subtracted from the value for the hand wash will provide an estimate of exposure to the hands when chemical resistant gloves are worn.

**Table 3. The Average Daily Exposure to Bensulfuron Methyl For Mixer/Loaders and Applicators Making Applications to Rice**

WORK TASK (worker #)	AVERAGE DAILY BENSULFURON METHYL EXPOSURE (a,b) (ug of exposure/lb of a.i. applied)							AVERAGE LBS A.I. APPLIED PER WORKDAY	TOTAL DAILY EXPOSURE (c) (mg)
	foam filter	hand wash	face/neck	arms	upper body	lower body	total		
<b>Pilots</b>									
site 1	0.66	18.5	3.2	22.6	12.1	38.9	96.0	28.7	2.76
site 2	0.12	4.3	0.5	7.4	3.0	4.1	19.4	25.7	0.50
site 3	0.58	14.0	3.0	50.9	8.9	19.9	97.3	26.6	2.59
AVERAGE	0.42	11.5	2.1	25	7.5	19.3	66	27	1.95
<b>Mixer/Loaders</b>									
site 1	1.07	25.6	3.7	62.7	8.8	24.3	126.2	28.7	3.62
site 2	0.56	5.4	1.6	25.4	1.7	2.0	36.7	25.7	0.94
site 3	1.54	29.9	4.0	43.1	9.4	19.6	107.5	26.6	2.66
AVERAGE	1.01	18.8	3.0	41.9	6.1	14.0	85.0	27	2.47
<b>Flaggers</b>									
site 1	0.70	27.1	16.3	67.0	14.2	13.0	138.3	28.7	3.93
site 2	0.20	1.4	1.3	5.9	2.0	0.8	11.6	25.7	0.30
site 3	0.45	6.9	3.5	34.1	6.6	36.1	87.7	26.6	2.33
AVERAGE	0.43	10.7	6.5	32.7	7.0	15.1	72.0	27	2.19

Haskell, WH&S, 1993

(a) Each value represents the average amount of Londax found on each sample matrix for those workdays at the site.

(b) The "AVERAGES" take into account three consecutive workdays at sites 1 and 3 and four consecutive workdays at site 2.

(c) The TOTAL DAILY EXPOSURE (mg) was calculated as the total AVERAGE DAILY LONDAX EXPOSURE (ug) per lb a.i. applied multiplied by the AVERAGE LBS A.I. APPLIED PER WORKDAY divided by 1000 (ug/mg).

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Table 4. Estimated Exposure for Pilots, Mixer/loaders, and Flaggers as Mitigated by the Whip® IEC Label<sup>a</sup>

Task	Pre-Mitigation µg/lb a.i. applied			Post Mitigation <sup>(d)</sup> µg/lb a.i. applied		
	Body	Hands	Inhalation	Body	Hands	Inhalation
Pilot	54 (56)	65 <sup>(b)</sup> (67)	0.37 (0.44)	54 (56)	3.9 <sup>(e)</sup> (4.0)	0.37 (0.44)
Mixer/Loader	65 (34)	19 <sup>(c)</sup> (13)	1.0 (0.70)	3.3 <sup>(f)</sup> (1.7)	19 (13)	0.10 (0.035)
Flagger	62 (52)	11 (13)	0.43 (0.41)	62 (52)	0.64 <sup>(e)</sup> (0.76)	0.43 (0.41)

- (a) - The exposure data was derived from the results of the bensulfuron-methyl study in Table 3. The arithmetic mean and standard deviation (s) of 9 or 10 individuals for each work task are shown.
- (b) - The pilots wore cotton or leather gloves during the study. However, the bensulfuron-methyl label does not require the pilots to wear gloves. A study by Maddy et al. (1984) indicates that exposure to the hands of pilots not wearing gloves represents 54.5% of the total exposure. The observed exposures in the study were corrected with the following equation:  $X(0.455-X) = Y$  where X equals the body exposure except hands and Y equals the corrected exposure to the hands.
- (c) - The mixer/loaders were wearing chemical resistant gloves during the study.
- (d) - Mitigation provided by fenoxaprop-ethyl label is different than the surrogate exposure study (bensulfuron- methyl).
- (e) - Chemical resistant gloves were observed to reduce exposure to fenoxaprop-ethyl by 94%. Values were multiplied by 0.06.
- (f) - The whole body protection provided when workers wear either work clothing underneath a chemical resistant suit and chemical resistant gloves or wear work clothing, chemical resistant gloves and use a closed system to mix and load is 95%. The values have been multiplied by 0.05.

**Table 5. Estimate for Mitigated Daily and Seasonal Exposure to Fenoxaprop-Ethyl for Pilots, Mixer/loaders, and Flagger Making Applications to Rice**

Work Task	Average Daily Exposure <sup>(a, b)</sup> ( $\mu\text{g}/\text{lb}$ of a.i. applied)		lbs of Active Ingredient Applied per Workday <sup>(c)</sup>	ADD <sup>(d)</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )	SADD <sup>(e, f)</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )
	Dermal	Inhalation			
<b>Aerial Application:</b>					
Pilot					
mean (arth.)	58	0.37	72	40	17
(+1SD)	120	0.81	72	83	----
(+2SD)	180	1.3	72	130	----
Mixer/loader					
mean (arth.)	22	0.10	72	26	11
(+1SD)	37	0.14	72	36	----
(+2SD)	52	0.17	72	46	----
Flagger					
mean (arth.)	63	0.43	72	44	19
(+1SD)	120	0.84	72	83	----
(+2SD)	170	1.3	72	120	----
<b>Ground Application:</b>					
Mix/Load/Apply					
and Clean-low	----	----	----	1.0	0.29
High	----	----	----	22	6.3

- (a) - The value for the Average Daily Fenoxaprop-Ethyl Exposure for each work task was taken from Table 4.
- (b) - The exposure estimate when workers wear long pants and long-sleeved shirt and chemical resistant gloves and the mixer/loader uses a closed mixing/loading system. **Fifteen  $\mu\text{g}/\text{lb}$  a.i. of dermal exposure has been added to the mixer/loader from cleaning the airplane.**
- (c) - The fenoxaprop-ethyl acreage treated by air is equivalent to the acreage treated in bensulfuron-methyl study (538 acres per workday) reduced by 33% to reflect the greater minimum dilution rate (10 gallons per acre) for applications to rice and the label rate of 3.2 oz. a.i. per acre for Whip<sup>®</sup> IEC Herbicide.
- (d) - The Absorbed Daily Dosage (ADD) includes material from dermal and inhalation exposure. The percent of dermal absorption is 73%. Inhalation uptake is assumed to be 50% with 100% absorption (Raabe, 1988). The applicator exposure studies were conducted on male workers and the assumed body weight was 76 kg.
- (e) - The ADD multiplied by the annual number of exposure days, then divided by the season of use- 35 days.  
Exposure days:  
1. Aerial application- 15 days (Jones, 1993).  
2. Ground application- 10 days (Haskell, 1993).
- (f) - Since the subchronic toxic effect may occur only after a series of exposures, the mean value alone is appropriate for calculating the Seasonal Absorbed Daily Dosage (SADD).