1-21-85

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

004239

MEMORANDUM

SUBJECT: PP#4E2983 Proposed Tolerances for Fenthion in/on Whole Grapefruit, Oranges and Mangoes.
CASWELL No. 456F Acc. No. 072022

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: George LaRocca, PM #15
Insecticide-Rodenticide Branch/RD (TS-767)

THRU: R. Bruce Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769) 1/14/85

FROM: George W. Robinson, D.V.M. Geo. W. Robinson 1/11/85
Review Section 1
Toxicology Branch/HED (TS-769) 1/21/85

Action Requested:

The petitioner, Mobay Chemical Corporation Agricultural Chemicals Division, proposes the establishment of tolerances for residues of Fenthion (O,O-Dimethyl-O-[3-methyl-4-(methylthio)-phenyl] phosphorothioate) from application of the formulation LEBAYCID 40 E.C. insecticide in or on the raw agricultural commodities whole grapefruit, whole oranges and whole mangoes at 1.0 ppm. This action would amend Section 180.214, 40 CFR. The requested tolerances would cover residues of fenthion from treatment of these commodities outside of the United States.

Recommendation:

Toxicology Branch objects to the establishment of the proposed tolerances of 1.0 ppm for residues of Fenthion in or on the raw agricultural commodities grapefruit, oranges and mangoes. Existing toxicity data do not support establishment of these tolerances.

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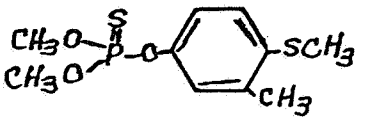
Structural Formula:



0,0-Dimethyl 0-[3-methyl-4-(methylthio)phenyl]phosphorothioate

*Inert ingredients in Lebaycid 40 EC have been cleared under 40 CFR 180.100160. There are no known regulatory actions against registration of LEBAYCID 40 EC (Fenthion) and it does not appear on an RPAR list.

Proposed Use:

LEBAYCID 40 EC (EPA Reg. No. 3125-197), will be used for the control of Mexican fruit flies and citrus white flies in grapefruit, orange and mango crops. A dosage of 5 fl oz. (2.1 oz ai)/acre or 12.4 fl oz. (150 gm ai)/hectare diluted in water and applied as a foliar spray for a maximum of 3 applications to grapefruit and oranges and 4 to mangoes with a pre-harvest interval of 7 days.

Previously Submitted Toxicity Data:

The following toxicity data were selected from a review (dated 2/2/68) and a summary (dated 2/6/6), both by R.D. Coberly which cited no PP Nos. These studies were not available for evaluation and are therefore not CORE graded.

Baytex:

1. 16-week feeding, rat, ChE NOEL = 3 ppm, ChE LEL = 5 ppm.

2. 1-yr. feeding, rat, ChE NOEL = 3 ppm, ChE LEL = 5 ppm.

3. 1-yr. feeding, dog, ChE NOEL = 2 pm (LDT), ChE LEL = 5 ppm.

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Newly Submitted Toxicity Data:

Fifty-two individual reports were submitted in support of this petition. Whether any of these studies were previously reviewed by a federal agency could not be determined since the review (2/2/68) mentioned above contains no means of identification such as PP#s, authors, Acc. Nos., laboratories and dates of study reports. Summaries, a few publications and scientific articles, with no detailed or raw toxicity data, comprise the overwhelming majority of these reports. There are several complete studies with data considered adequate enough for in-depth reviews.

Toxicological Testing of BAY 29493 by O.R. Klimmer, University of Bonn, West Germany, Report No. 11,600, 3/25/63, Acc. No. 072022.

1. Acute Oral Toxicity to Rats

Test Materials:

a. Bayer 29493 - pure (99%)
b. Bayer 29493 - technical Pt. 57 (97.4%)
c. Bayer 29493 - technical Pt. 58 (97%)

Test Animals: Male Wistar- CFN rats, weighing 130-150 g., 5/dose group.

Route of Administration: Oragastric by stomach tube.

Results:

a. Bayer 29493-pure (99%) in 11 doses ranging from 140-550 mg/kg bw.
Acute oral LD_{50} = 315 mg/kg bw in male rats
Toxicity category II; Core-Minimum.

b. Bayer 29493-tech. Pt. 57 (97.4%) in 9 doses ranging from 155-400 mg/kg bw.
Acute oral LD_{50} = 241 mg/kg bw. in male rats.
Toxicity category II; Core-Minimum.

c. Bayer 29493-tech. Pt. 58 (97%) in 10 doses ranging from 155-450 mg/kg bw.
Acute oral LD_{50} = 268 mg/kg bw in male rats.
Toxicity category II; Core-Minimum.

These studies contained the minimum data necessary for calculation of LD_{50} for males. Acute oral LD_{50} study in females is not necessary since results of Acute Dermal Study in females, together with previously reviewed acute oral data for females (Coberly, 1968) demonstrate that females are no more sensitive than males to fenthion.

2. Dermal Toxicity of Rats

Test Materials: Bayer 29493 technical (Pts. 57 and 58)

Test Animals: Male Wistar rats weighing 150-180 g., 5/dose group.

Route of Administration: Massaged into skin on shaved backs.

Results:

a. Bayer 29493 technical Pt. 57, undiluted in 8 doses ranging from 200-600 mg/kg bw.
Acute dermal LD_{50} = 410 mg/kg bw in male rats.
Toxicity category II; Core-Minimum.

b. Bayer 29493 technical Pt. 58, undiluted in 8 doses ranging from 200-600 mg/kg bw.
Acute dermal LD_{50} = 345 mg/kg bw in male rats.
Toxicity category II; Core-Minimum.

3. Acute Toxicity to Rats (Lebaycid)

Test Material: 50% Preparation Lebaycid from batch No. Fl. 308-60.

Test Animals: Male Wistar-CFN rats weighing 130-150 g. 5/dose group.

Route of Administration: Oragastric by stomach tube in 8 doses ranging from 100-400 mg/kg bw.

Results: Acute oral LD_{50} = 242.5 mg/kg bw (males).
Toxicity category II; Core-Minimum.

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4. Acute Dermal Toxicity to Rats (Lebaycid)

Test Material: Lebaycid (50% a.i.)

Test Animals: Male Wistar CFN rats weighing 150-180 g. 5/dose group.

Route of Administration: Rubbed into skin of shaved backs in 10 doses ranginf from 400-1200 mg/kg bw.

Results: Acute dermal LD_{50} = 730 mg/kg bw. in male rats. Toxicity category II; Core-Minimum.

S 1752 Determination of Percutaneous Toxicity by F. Mihail, Bayer AG Institut fur Toxikologie, Rep. No. 7604, 6/12/78; Acc. No. 072022.

Test Material: S 1752 technical (98.2% pure).

Test Animals: Male and female Wistar rats weighing 200 to 240 g, 10/sex/dose group.

Route of Administration: Applied undilduted to intact clipped dorsal skin in 6 doses ranging from 500-3500 mg/kg bw. to male rats and in 5 doses ranging from 1500-5000 mg/kg bw. to female rats.

Results: Acute dermal LD_{50} = 1680 mg/kg bw. (male).
Acute dermal LD_{50} = 2830 mg/kg bw. (female).
Toxicity category II; Core-Minimum.

S 1752 (Fenthion) Subacute Dermal Cumulative Toxicity Study on Rabbits (Study No. S 1752/004) by F. Mihail and B. Schilde, Bayer AG Institut fur Toxikologie, Wuppertal, W. Germany, dated 9/7/79. Acc. No. 072022.

Test Compound: Technical S 1752 (Fenthion, the active ingredient of Liebaycid® and Baytex®; purity, 98.2%.

Test Animals: Male and female New Zealand white rabbits weighing 2.8 to 3.3 kg, bred by Hacking and Churchill Ltd., Huntingdon, England.

Experimental Design:

Rabbits were caged singly under controlled temperature and ventilation and a 12-hour light/dark cycle with feed and water ad libitum. Rabbits were assigned to one of 3 groups of 6 males and 6 females each and received doses of the test compound as follows: 0 (control), 5 and 25 mg/kg body weight. Rabbits were weighed prior to treatment and at the end of each week of testing.

The backs and flanks of each rabbit were clipped free of hair 48 hours prior to treatment; test areas of the skin were abraded in half of the males and females per test group 24 hours prior to treatment. The test compound was formulated with 1.5% Cremophor EL (v/v) in distilled water and applied to back and flank test skin areas (approx. 5x5 cm) once each workday (5x per week) for 3 weeks. The animals were immobilized and restrained during dosing and a 7-hour exposure period. Treated skin areas were washed with soap and water at the end of each exposure period. Growing hair was clipped once each week.

All rabbits were observed daily for general appearance, behavior, appetite and feces. Treated skin sites were examined before and after daily applications with scoring based on Draize. Skinfold thickness at the center of test sites was measured with skin calipers.

Blood and urine samples were collected from all rabbits prior to testing and at termination of treatment for hematology, blood chemistry and urinalysis. The rabbits were sacrificed 24 to 48 hours after final treatment and underwent gross pathological examination during necropsy. Organ weights were recorded for adrenals, heart, kidneys, liver, lungs, spleen, testes or ovaries, and thyroid. Tissue samples, including skin, were fixed, stained and examined histopathologically.

Results:

There were no compound related variations in external appearance, behavior, appetite, consistency and appearance of feces, and body weight gains/losses by individual animals during the 3-week test period.

Slight to moderate erythema and edema were observed in all animals with abraded skin even prior to treatment. Pustules occured in 12 treated and control rabbits with abraded skin and in 5 treated and control rabbits with intact skin. Skinfold thickness and skin inflammation decreased during the first week of the experiment and healed completely during the second week with formation of scabs.

No dose-group specific differences were observed in urinalysis, hematology and clinical chemistry (blood). Alkaline phosphatase levels were lower and blood urea was higher at termination in all animals than at the beginning of the test. Cholinesterase activity was significantly inhibited in blood plasma and erythrocytes of rabbits (M & F) at the 5 and 25 mg/kg doses during the treatment period. Cholinesterase activity in brain at the high dose level (25 mg/kg) was also significantly depressed, compared to controls.

Gross examination at necropsy detected 11/36 rabbits with pulmonary edema and 21/36 rabbits with kidney lesions (e.g., pitted areas or cysts) which were unrelated to treatment. Absolute and relative organ weights were similar in test and control groups. However, lung weights varied a great deal probably due to the presence of pulmonary edema. Histopathology revealed no test compound related changes or lesions in examined organs. Slight to moderate cellular infiltrations were observed sporadically in the dermis of individual rabbits with slightly thickened skin (mechanical irritation) in all groups.

Conclusion:

No signs of systemic toxicity occurred from 15 dermal applications of fenthion technical S 1752 (98.2% a.i.) during a 3-week period at doses up to 25 mg/kg day.

NOEL > 25 mg/kg/day (other than ChE)
ChE NOEL < 5 mg/kg/day

Classification: Supplementary - No demonstrated NOEL for ChE inhibition (plasma and RBC).

Fenthion Chronic Toxicity Study on Dogs (Two-year feeding experimental) by K. Hoffman and C.H. Weischer, Bayer AG Institute fur Toxikologie, Report No. 5737, Nov. 20, 1975, Acc. No. 072022.

Test Compound: Fenthion (S 1752), as a 50% premix prepared with Wessalon S, Lot No. 1234.

Test Animals: Purebred Beagle dogs (males and females) supplied by Velaz Breeding Association, Czechoslovakia, weighing 5.5 to 7.9 kg., 19 to 21 weeks old.

Experimental Design:

Eight dogs (4 M & 4 F) were randomly assigned to each of four groups: 0 (control), 3, 10, and 30-60 ppm. Pulverized dry food was blended with the test compund to yield the appropriate concentration levels. All dogs were fed 250 grams daily in weeks 1 and 2, 300 grams daily in weeks 3 and 4 and 350 grams daily in weeks 5 through 104. The high dose group recieved dietary concentrations of the test compound as follows: 30 ppm from week 1 to week 64; 50 ppm from week 65 to week 67; and, 60 ppm from week 68 to week 104. Food not consumed within 24 hours was determined prior to the next daily feeding.

All dogs were observed daily for physical appearance and behavior. Body weights were recorded weekly for each dog during the first 52 weeks and bi-weekly thereafter. In depth examinations (including pupillary reflex, patella reflex, flexor reflex, electrocardiographic and ophthalomologic examination) were conducted at 13-week intervals throughout the study. Blood samples were collected prior to testing, bi-weekly from 3 to 13 weeks, and at subsequent 13-week intervals thereafter for hematology and clinical chemistry. Individual urine samples were collected at 13-week intervals. The study was terminated at 104 weeks and all dogs underwent necropsy and gross pathological examination. Organ weights were recorded for brain, heart, lung, liver, spleen, kidneys, pituitary, thyroid, adrenals, gonads, prostate and pancreas. These organs and the following organs and tissues were fixed and processed for histopathological examination: epididymides, uterus, parotid, colon, mesenteric lymph nodes, gall bladder, urinary bladder, eyes, optic nerve, femoral nerve, aorta, skeletal muscle (quadriceps), bones (femur) and bone marrow (sternum).

Results:

Data on all aspects of the study were provided for each experimental animal. No differences in physical appearance and behavior were observed among treated and control groups. All dogs survived the duration of the study in a state of good general health with no clinical signs of toxicity. There were variable individual differences in food consumption in all dosage groups which appeared to be unrelated to dietary concentrations of test material. Body weight gain was similar in treated and control groups throughout the study.

Periodic ophthalmoscopic examinations, electrocardiograms, hematological values, clinical chemistry determinations and urinalysis revealed no changes ascribable to dietary concentrations of fenthion.

Plasma cholinesterase activity was markedly suppressed in dogs of both sexes at 10 ppm (-30%) and 30-60 ppm (-60%) dosage levels. Erythrocyte cholinesterase inhibition was also marked in male dogs at 10 ppm (-20%) and 30-60 ppm (-40%) dosage levels. In female dogs, erythrocyte cholinesterase inhibition occurred only at the 30-60 ppm (-20%) dosage level. Terminal brain cholinesterase inhibition was significant at the 30-60 ppm dosage level in dogs of both sexes.

Gross pathological examination at necropsy revealed no dose/compound-related changes. Absolute and relative organ weights were similar in treated and control groups, except that: the four female dogs at 10 ppm were in estrus and had somewhat heavier ovaries. Histopathological examination revealed no alterations/abnormalities which were dose/compound-related. The histopathological data reported in this study are quite limited and nonsepcific concerning lesions present, however. A greater variety of specific lesions should be observed in a 2-yr. feeding study than hypertrophy/hyperplasia, hypoplasia, metaplasia, parasitic lesion, cell or inflammatory cell infiltrations, cystic alterations and dilatation.

Conclusion:

More detailed data from the histopathology as performed are necessary for an adequate toxicological evaluation of the 2-yr. chronic effects of fenthion in dogs.

Classification: Core-Supplementary.

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BAY 29498 Generation Tests on Rats by Eckhard Loser, Bayer AG Institute of Toxicology, May 2, 1969, Report No. 1400, Acc. No. 072022.

Test Compound: Bay 29493, technical active ingredient of Fenthion, purity grade of 96.1%, formulations known under the commerical name LEBAYCID.

Test Animals: Rats of the breed FB_{30} (stock Elberfeld), approx. 33 days old, weighing 45-55 g.

Experimental Design:

The rats were assigned to 4 test groups (10 males and 20 females) and received Bay 29493 mixed into the feed as follows: 0 (control), 3, 15 and 75 ppm. Rats were caged singly until mating with feed and water ad libitum. Bay 29493 was mixed into the feed once a week. Rats consumed their respective concentrations of Bay 29493 during the total duration of the test, including juvenile growth period, mating period, gestation, and duration of rearing of the young. At puberty (approx. 100 days of age) 2 female rats were caged with 1 male rat during a mating period of 19 or 20 days. Male rats were interchanged such that each female had contact with 3 different males during the mating period. After mating, all rats were again caged singly.

Immediately after birth the number and weights of the offspring were recorded. Offspring were closely observed macroscopically for deformities immediately after birth and also during the subsequent rearing period. After 5 days, litters with more than 10 young rats were reducted to 10. The weight of each reduced litter was recorded once a week thereafter. Offspring of the first pairing were reared to 4 weeks of age and sacrificed (F_1a, F_2a, & F_3a - generations).

Male and female rats of the F_0-(parental) generation were paired for mating a second time as described above. Offspring from the second pairing of this and subsequent generations were reared to 4 weeks of age. They were then separated by sex. At the age of 8 weeks 10 male and 20 female rats were selected from respective dosage groups and fed Bay 29493 at the proper concentrations. At the age of 100 days animals were paired as described. Mating, gestation and rearing of offspring occurred the same as described above. All animals of the F_0-, F_1b, F_2b and F_3b generations were sacrificed thereafter.

At sacrifice and necropsy, the following tissues from all experimental rats were fixed, sectioned and stained for histopathological examination: heart, kidneys, gonads, liver, adrenals and thymus. All tissues that were considered to be within normal limits were not reported.

Results:

All submitted data for this study were in summary form (average and total numbers). The following specific data needed to construct as reproductive performance chart, were not present in this report:

1. information on individual dams,
2. information on individual litters per dose level,
3. information on individual pups,
4. number of pups per litter for individual dams at each dose level,
5. number of litters per dose level,
6. food consumption,
7. individual body weights for parents and progeny in each generation.
8. the pathology report is incomplete with insufficient detail.

Based on the summary data as presented, the following observations could be made:

1. Mean body weights of both male and female rats of the high-dose group (75 ppm) in the F_0 - generation (original parental) were signficantly lower than those of control (0 ppm), low- (3 ppm), and mid-dose (15 ppm) groups from shortly after weaning through maturation, mating and gestation periods to termination of the test.

2. The average number of pups per litter at birth in the F_1a - generation was about 33% less in the mid- and high-dose groups than in low-dose and control groups. In all other generations (from F_1b to F_3b), the average number of pups per litter at birth were similar in control and test groups.

3. Mean body weights of offspring (male and female) of the 3 subsequent generations were similar from birth to weaning at 4 weeks of age at all dose levels. F_1b generation rats of both sexes at the high- dose level had lower body weights than other dose and control groups, during maturation, mating and gestation periods. In the F_2b - generation body weights did not differ appreciably from controls for any dose group from weaning through the duration of the test.

Conclusions:

Chronic ingestion of BAY 29493 by rats in doses up to 75 ppm in feed over 4 generations did not appear to have any adverse effects on reproduction. However, adequate toxicological evaluation cannot be made without raw data which is listed in the first paragraph under "Results".

Classification: Core-Supplementary

Recommendation:

The registrant should submit the raw data, if available, as listed in the first paragraph under "Results". Toxicological evaluation of such data may alter the classification of this multi-generation rat reproduction study.

Embryotoxicity and Teratogenicity Study: S 1752 in Rabbits - Final Report by H. Becker, E. Mueller, H. Lind and Ch. Terrier, Research & Consulting Co., Ltd., Itingen, Switzerland, RCC Proj. 004961, dated 9/17/82. Acc. No. 072022.

Test Material: S 1752 (Fenthion; Lebaycid R; Baycid R; Baytex R), Batch No. P. T. - No. 230 102 069, Technical active substance 93%, yellow-brownish liquid received 12-14-81.

Test Animals: Rabbits, Chinchilla Hybrid, 4 to 6 months old, weighing 2.4 to 3.6 kg.

Experimental Design:

Animals were acclimated and kept under hygienic, controlled (air conditioned) laboratory conditions, with pelleted standard diet and water ad libitum throughout the experiment. Feed and water were analyzed from contaminants.

Female and male rabbits were mated in a 1:1 ratio twice, if possible, by the same male as soon as possible after the initial mating. The day of mating became gestation day 0. Mated females were randomly assigned to 4 groups of 20 each and received the following doses of test material: vehicle control (0), 2, 6 and 18 mg/kg b. wt. respectively. Test material was suspended daily in a 2% solution of carboxymethycellulose natriumsalt using a homogenizer and/or magneic stirrer to attain the indicated dose levels in a volume of 4 ml/kg body weight. Stability of the test material was chemically analyzed prior to commencement of the study.

All test animals were individually identified by number on ears and by cage number. Vehicle and test material suspensions (at respective concentrations) were administered orally by gavage in a volume of 4 ml/kg body weight to all mated females from days 6 through 18 of gestation. All animals were observed twice daily for mortality, signs and symptoms and individual body weights were recorded daily. Food consumption was recorded on days 6, 11, 15, 19, 24 and 28 of gestation.

All gravid dams were sacrificed on day 28 of gestation. The dams' organs, especially reproductive, were examined and corpora lutea were counted. Fetuses were removed by caesarean section and uterine contents were examined (placentae, amniotic fluid, mucosa, resorptions, abortions). All fetuses were weighed and examined externally and internally. The heads of fetuses were fixed and sliced for examination of the brain and cephalic viscera. The trunks of fetuses were cleared and stained for skeletal examinations.

Results:

No clinical symptoms or signs of toxicity were observed in females of vehicle control, low- and mid- dose groups. A variety of symptoms were recorded for females in the high- dose group after 6 days of dosing (12 days post-coitum). All 20 females became dyspneic, 11 developed diarrhea, and 12 had marked salivation. Other symptoms which occurred sporadically in the high- dose group were melena, wheezng, clonic muscle spasms, abortion and coma. Eleven (11) high- dose females died between 8 and 13 days post- treatment (14 to 19 days post-coitum).

Food consumption and bodyweight gain were much less in the high- dose group than in vehicle control, low- and mid- dose groups.

The number of pregnant females, implantations per dam and live fetuses were similar in vehicle control, low- and mid-dose groups. Implantations per dam and number of live fetuses were also similar in vehicle controls and the 5 surviving gravid dams in the high- dose group at termination (11 died and 4 either did not conceive or aborted during the study). Data on animals that died or aborted were not presented in the report. Autopsy findings of high- dose females that died during the study listed only 2/11 with fetuses (12 in one; 10 in the other). This provides evidence of conception in only 7/20 females in the high dose group. The rate of fetal resorptions were higher in the mid- and high- dose groups than in vehicle controls. Mean body weights of fetuses were significantly lower in the high- dose group than in vehicle controls. No relevant pattern of occurrences of visceral, skeletal and cephalic malformations and anomalies was reported for the vehicle control and treated groups.

[redacted]

Conclusion:

In the high- dose group (18 mg/kg/day), maternal mortality was 55% and the documented conception rate was only 35%. Fetal resorption rates were higher at 6 and 18 mg/kg/day than in vehicel controls. Fetal and maternal bodyweights were lower in the high- dose group than in vehicle controls.

Fetotoxic NOEL = 2 mg/kg/day; LEL = 6 mg/kg/day
Teratogenic NOEL = 18 mg/kg/day
Maternal toxicity NOEL = 6 mg/kg/day

Classification: Core - Minimum Data.

S 1752 (Fenthion: ®Lebaycid Active Ingredient) Dominant Lethal Study on Male Mice To Test For Mutagenic Effects by Dr. L. Machemer, Bayer AG Institut fur Toxikologie; Report No. 7449 dated 4/10/78, Acc. No. 072022.

Test Material: S 1752 (fenthion), rcvd. 1/75, purity of 98.1%.

Test Animals: Mice of the NMRI strain bred and supplied by S. Ivanovas GmbH, Kisslegg/Allgau; males weighed 33 to 37 grams and females weighed 25 to 33 grams; mice were about 11 weeks old.

Experimental Design:

The mice were housed in cages under standard laboratory conditions with food and tap water ad libitum.

Two experiments were conducted using 50 treated male mice; females used in the study were not treated. In Experiment I 50 male mice received a single oral dose of 25 mg of S 1752/Kg bodyweight in a 2% Cremophor EL emulsion by gavage. A vehicle control group of 50 male mice was given 2% Cremophor EL emulsion, only, by gavage. Each treated and control male immediately was caged with one untreated virgin female for a 4-day mating period, at which time this mated female was removed and caged singly and replaced by another virgin female.

A series of 4-day mating periods were repeated with each male for a total of 12 matings over 48 days. Mated females were sacrificed 14 days postcoitum and the uterus and its contents of each female were examined for total implantations, live and dead implants and resorptions to determine pre- and post-implantation losses.

Another group of 50 male mice received 10 mg/kg bw in Experiment II because of the degree of toxicity observed in Experiment I; all other aspects of the study were repeated.

Statistical analyses used in this study was reported by Dr. L. Machemer as follows:

"The number of dead implants and all implantations (square root transformed) and the ratio of dead implants to total implantations (angular transformed) were evaluated by the two-factor analysis of variance. If the F-test showed significane ($p < 0.05$) for the factors dose and time, the least signficant difference was determined by the TUKEY test...The contrasts between the variants (control, test compound) and the alterations with time were evaluated by the method of orthogonal comparisons... In addition, the frequency distributions of different parameters (total implantations, dead implants, live implants) in the treated group and the control group were compared by means of the non-parameteric KOLMOGOROV-SMIRNOV test".

Individual data for all mated females were provided for Experiments I and II.

Results:

Treated male mice in Experiment I exhibited drowsiness and ruffled coat. Three treated male mice died during the first mating period and 1 more treated male mouse died during the second mating period. Three deaths occurred in untreated mated females: 1 mated with an untreated male (control); and 2 mated wtih treated males. These losses resulted in the examination of 599 females in the untreated group and 551 females in the S 1752 treated (25 mg/kg bw group). Treated male mice in Experiment II (10 mg/kg bw) had no signs or symptoms of toxicity and no deaths occurred. Four deaths did occur in untreated mated females: 2 mated with untreated males (control); and, 2 mated with treated males. These losses resulted in the examination of 598 females in both the control and S 1752 treated (10 mg/kg bw) groups.

Fertilization rates were unaffected for males treated with S 1752 in both experiments. Actually, treated males had higher fertilization rates than control males in most mating periods.

Sporadic variations occurred among females which were mated to treated and control males for the following: total implantations, pre- and post-implantation losses, and live and dead implants. These variations were within the normal range for the control group and considered to be of no biological significane, except, among females bred to treated males in mating periods 1 and 2 in Experiment I (25 mg/kg bw). Total implantations and live implants were significantly less and pre-implantation losses were significantly greater in the treated group than in controls mated in periods 1 and 2 in Experiment I. These differencs could possibly be an indirect treatment related effect due to the condition of males which received the moderately toxic dose of 25 mg/kg bw S 1752.

There was no post-implantation lethal effect observed in any of the treated groups.

Conclusion:

Single oral doses of 10 and 25 mg/kg bw S 1752 (Fenthion) in male mice of the NMRI strain not produce a primary mutagenic effect based upon the stated criterion in this dominant lethal study. Signs of systemic toxicity occurred in male mice at the high dose level with 4/50 deaths (8% mortality).

Non-mutagenic up to 25 mg/kg bw.
Moderately toxic @ 25 mg/kg bw.
Systemic NOEL = 10 mg/kg bw.

Classification: Acceptable

Micronucleus Test on Mouse to Evaluate S 1752 for Mutagenic Potential by B. Herbold, Bayer Ag Institut fur Toxikologie, Rep. No. 9577, 11/26/80; Acc. No. 072022.

Test Material: S 1752, Fention, batch 230802056; a.i. of Lebaycid; purity of 98.5-98.9%.

Test Animals: Mice, NMRI strain, supplied by F. Winkelmann, Borchen.

Experimental Design:

Mice, weighing 25-38 g, 8-12 weeks old were randomly assigned to test and control groups of 10 mice each (5/sex) and housed separately by sex and test group with no more than 3 mice/cage under controlled temperature and relative humidity with feed and water ad libitum.

S 1752 was suspended in a 0.5% Cremophor emulsion received by 2 test groups at doses of 50 and 100 mg/kg. A negative control group received the emulsifier only. Endoxan dissolved in demineralized water was received by a positive control group at 145 mg/kg. Test and control groups received the respective material orally by gavage in 2 doses at a 24 hour interval. All mice were sacrificed 6 hours after the second doses and femoral bone marrow smears were prepared.

Polychromatic and normochromatic erythrocytes were counted for each mouse using a microscope. The incidence of polychromatic erythrocytes with micronuclei and the ratio of the number of normachromatic erythrocytes per 1000 polychromatic erythrocytes were determined.

Results:

Clinical signs of toxicity (dyspnea, swollen eyes and loss of weight) were observed in 6/10 mice in the high dose group. Other mice appeared normal and there was no mortality in any group.

The incidence of micronucleated polychromatic erythrocytes were similar in the negative control and test groups indicating that S 1752 exerted no mutagenic effect at test levels. the number of micronucleated polychromatic erythrocytes in the positive control group (Endoxan) was significantly higher than in the negative control group. The ratio of polycromatic to normochromtic erythrocytes was not affected in test and control groups.

Conclusion:

Two 100 mg/kg bw doses of Fenthion within 24 hours were not mutagenic to mice in the micronucleus test.

Classification: Acceptable

Bioassay of Fenthion for Possible Carcinogenicity (Rats) by Gulf South Research Institute, NCI-CG-TR-103 (DHEW Publ. No. (NIH) 79-1353), 1979.

Test Material: Fenthion (technical), Lot No. 4050284 from Chemagro Division of Mobay Chemicals.

Test Animals: Rats, strain F344 supplied by NCI Frederick Cancer Research Center.

Rats were caged individually under controlled temperature and ventilation with 10 hours lighting per day and feed and water ad libitum.

The required amounts of fenthion were dissolved in acetone and added to the feed (Wayne lab Blox meal) for dosed rats. Corn oil at 2% w/w was then added to the treated and untreated feed (for control rats) as a dust suppressant. The diets were mixed for at least 25 minutes to obtain homogeneity and to permit the acetone to evaporate. Formulated diets were prepared weekly.

A 13-week subchronic feeding study utilizing 10 rats/sex/dose with 7 doses ranging from 5-320 pm fenthion was conducted to estimate the maximum tolerated dose (MTD). Body weight gain was supressed in both sexes at 320 ppm with one death occurring in females. The MTD appeared to be 160 ppm. The report states that "In previous bioassays of organophosphorus chemicals at this laboratory, chronic doses based on subchronic tests were toxic. Thus, relative low concentrations (10 and 20 ppm) were set for the chronic study".

Six-week old rats were placed on the chronic feeding study in groups that received the test material as follows: 25/sex at 0 and 50/sex each at 10 and 20 ppm. All rats were observed twice daily for toxic signs and weighed at 2-week intervals. More detailed examinations were performed monthly inlcuding palpation for masses. Animals found moribund were sacricied. All surviving rats were dosed for 103 weeks, observed 1-2 weeks thereafter, and sacrificed. Necropsies were performed on all animals including those found dead (except those in states of marked cannibalization or autolysis). The following tissues and all gross lesions were fixed, embedded in paraffin, sectioned, stained and examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, pancreas, stomach, small and large intestines, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate, uterus, testis, ovary, and brain. Blood smears were also prepared and examined.

Results:

Mean body weight gains and clinical signs were similar in dosed and control rats throughout the study. Survival of rats in this study was as follows:

Treatment	Week	Percent Survival	
		Male	Female
Control	103	84	64
Low Dose	103	64	76
High Dose	103	80	64

An adequate number of rats of each sex survived at each dose level to be at risk for late developing tumors.

C-cell adnomas of the thyroid occurred at a higher incidence in female rats of the low-dose group (12/48; 25%) when compared with female rats in the high dose (4/46; 8.7%) and control (2/22; 9.1%) groups; a dose-response relationship was not detected. The incidence of interstitial-cell tumors of the testes was 75%, 74% and 92%, respectively, in male rats in the control, low and high dose groups. The incidence of other neoplasms and noneoplastic lesions was comparable in treated and control rats of both sexes. However, the control group contained only 25 rats/sex compared to 50/sex in the dose group, thus making statistical interpretation of these results extremely difficult.

Conclusion:

Based on the low doses employed, the number of control rats tested, and the lack of a demonstrated toxic response, this study conducted by Gulf South Research provides insufficient evidence regarding the oncogenic potential of fenthion.

Classification: Supplementary

Carcinogenicity Classification: Inadequate evidence, Group D.

Bioassay of Fenthion for Possible Carcinogenicity (Mice) by Gulf South Research Institute, NCI-CG-TR-103 (DHEW Publ. No. (NIH) 79-1353), 1979.

Test Material: Fenthion (technical), Lot No. 4050284 from Chemagro Division of Mobay Chemicals.

Test Animals: Mice, strain B6C3F1 supplied by NCI Frederick Cancer Research Center.

Mice were housed at 5 females/cage and 2 or 3 males/cage under controlled temperature and ventilation with 10 hours lighting per day and feed and water ad libitum.

The required amounts of fenthion were dissolved in acetone and added to the feed (Wayne Lab Biox meal) for dosed mice. Corn oil at 2% w/w was then added to the treated and untreated feed (for control mice) as a dust suppressant. The diets were mixed for at least 25 minutes to obtain homogeneity and to permit the acetone to evaporate. Formulated diets were prepared weekly.

A 13-week subchronic feeding study utilizing 10 mice/sex/dose with 7 doses ranging from 5-320 ppm fenthion was conducted to estimate the maximum tolerated dose (MTD). Body weight gain was not affected and no mortality occurred in either sex at doses up to and including 320 ppm which is considered to be the MTD. The report states that "In previous biossays of organophosphorus chemicals at this laboratory, chronic doses based on subchronic tests were toxic. Thus, relatively low concentrations (10 and 20 ppm) were set for the chronic study."

Seven-week old mice were placed on the chronic feeding study in groups that received the test material as follows: 25/sex at 0 and 50/sex at 10 and 20 ppm. All mice were observed twice dairy for toxic signs and weighed at 2-week intervals. More detailed examinations were performed monthly including palpation for masses. Mice found moribund were sacrificed. All surviving mice were dosed for 103 weeks, observed 1 week thereafter, and sacrificed. Necropsies were performed on all animals including those found dead (except those in states of marked cannibalization or autolysis). The following tissues and all gross lesions were fixed, embedded in paraffin, sectioned, stained and examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, liver, salivary gland, pancreas, stomach, small and large intestines, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate, uterus, ovary, testis and brain. Blood smears were also prepared and examined.

Results:

Mean body weight gains were similar in the dosed and respective control mice throughout the study. A low incidence of clinical signs (alopecia, rough and discolored hair coats, and weight loss) occurred in dosed and control mice during the first year of the study. An increased incidence of clinical signs (alopecia, abdominal distension, tachypnea and pale mucous membranes) were noted in the dosed mice during the second year of the study. Survival of mice in this study was as follows:

Treatment	Week	Percent Survival	
		Male	Female
Control	103	88	96
Low Dose	103	60	78
High Dose	103	76	82

An adequate number of animals of each sex survived at each dose level to be at risk for late developing tumors.

Histopathologic findings revealed a higher incidence of several types of sarcomas of the skin and subcutaneous tissue in dosed mice than in controls, as follows:

Sarcoma Type (no. mice examined)	Control (25)	Low Dose (49)	High Dose (48)
Sarcoma, NOS	0	0	2 (4.2%)
Fibrosarcoma	0	4 (8.2%)	4 (8.3%)
Rhabdomyosacoma	0	3 (6.1%)	2 (4.2%)

The primary site for sarcomas, NOS and fibrosarcomas was considered to be the integument. Skeletal muscle within the subcutaneos tissue appeared to be the site of origin of the rhabdomyosarcomas. In two cases fibrosarcomas metastasized to the lungs and regional lymph node. One of the rhabdomyosarcomas metastasized to the regional lymph node and invaded the pararenal tissue. Incidences of these sarcomas (when combined) in the low- and high dose male mice in this study are 7/49 (14.3%) and 8/48 (16.7%), respectively. However, the incidence of sarcomas and fibrosarcomas in historical control male B6C3F1 mice used in bioassays of other chemicals tested at this same laboratory was 7/435 (1.6%), and no rhabdomyosarcomas occurred in historical control male or female B6C3F1 mice.

Conclusion:

The increased incidence of various types of sarcomas of the skin and subcutis in treated male B6C3F1 mice appeared to be associated with the administration of fenthion and suggested that fenthion was oncogenic in this sex and strain. However, the low doses employed, the inadequate number of control animals used and the lack of a measured toxic response prevent a clear determination of the oncogenic potential of fenthion to mice.

Classification: Core- Supplementary

Carcinogenicity classification: Inadequate evidence, Group D.

The following reports are brief summaries which contain insufficient detailed or raw toxicity data which are necessary for an adequate toxicological evaluation:

The Acute Oral and Dermal Toxicity of Two Samples of BAY 29493 by K.P. DuBois and F.K. Kinoshita, Toxicity Laboratory, University of Chicago, Illinois, 11-2-70; Acc. No. 072022.

Comparison of the Acute Oral Toxicity of BAY 29493 and Sumithion to Mice by K.P. DuBois, Toxicity Laboratory, University of Chicago, Illinois, 4-8-68; Acc. No. 072022.

The Acute Dermal Toxicity of TIGUVON Technical to Rabbits by D.W. Lamb and R.H. Anderson, Chemagro Division of Baychem Corporation, 8-22-74; Acc. No. 072022.

The Acute Dermal Toxicity of BAY 29493 Technical to Adult Female Mice by C.R. Crawford, R.H. Anderson and D.L. Nelson, Chemagro Corporation Research Department, 3-2-70; Acc. No. 072022.

S 1752 Acute Inhalation Toxicity Studies by J. Thyssen, Bayer AG Institute fur Toxikologie, Report No. 7842, 9-29-78; Acc. No. 072022.

Acute Inhalation Toxicity of Two Fenthion Samples to Rats by K.P. DuBois and W. Wong, Toxicity Laboratory, University of Chicago, 9-1-70; Acc. No. 072022.

S 1752 Test for Irritant Effect on Skin or Mucous Membrane by J. Thyssen, Bayer Ag Institute of Toxicology, 3-5-82; Acc. No. 072022.

Effects of Adding BAY 29493 in Combination with Other Choinergic Insecticides in the Diet of Male and Female Dogs by J. Deull, M. Root and J. Cowan, Department of Pharmacology, University of Chicago, 6-12-62; Acc. No. 072022

Subcutaneous, Intramuscular and Dermal Toxicity of Tiguvon to Dogs by C.J. Welter, Diamond Laboratories, Inc., 12-17-63; Acc. No. 072022.

Acute Toxicity of Injectable Tiguvon in Dogs by C.J. Welter and D.R. Johnson, Diamond Laboratories, Expt. No. TIG-1; Acc. No. 072022.

Determination of Acute Subcutaneous Toxicity of Injectable Tiguvon in Cats by C.J. Welter and D.R. Johnson, Diamond Laboratories, Expt. No. TIG-9; Acc. No. 072022.

Toxicity Screening Reports by C.E. Granito, U.S. Army Edgewood Arsenal, 3-1-65; Acc. No. 072002.

Acute Toxicity of Some Derivatives of Bayer 29493 to Female Rats by K.P. DuBois and A.B. Raymund, Department of Pharmacology, University of Chicago, 4-23-62; Acc. No. 072022.

3-Methyl-4-Methyl-Mercaptophenol (metabolite of Baytex) Acute Toxicity to Rats by Dr. Thyssen, Bayer Institute of Toxicology, 2-25-74; Acc. 072022.

The Acute Oral and Dermal Toxicity of a Liquid Formulation of Tiguvon by K.P. DuBois and F.K. Kinoshita, Toxicity Laboratory, University of Chicago, 10-27-70; Acc. No. 072022.

The Acute Oral and Dermal Toxicity of Tiguvon 7.6% Pour-On Concentrate to Rats and Rabbits by C.R. Crawford and R.H. Anderson, Chemagro Division of Baychem Corp., Ref. No. 73-123, 7-24-74; Acc. No. 072022.

The Acute Dermal Toxicity of BAY 29493 Technical and BAY 29493 4 lb/gal. SC to Rabbits by C.R. Crawford and R.H. Anderson, Chemagro Corporation, Ref. No. 69-115, 3-19-71; Acc. No. 0702022.

Acute Inhalation Toxicity of a Tiquvon Formulation by K.P. DuBois and W. Wong, Toxicity Laboratory, University of Chicago, 8-21-70; Acc. No. 072022.

The Interaction of Phenothiazine and Grubacides by D.L. Nelsom, Chemagro Corporation, Ref. No. 64-70, 11-3-66; 072022.

Additional Studies on Subacute Toxicity and Anthelmintic Efficacy of Tiquvon in Dogs by C.J. Welter and D.R. Johnson, Diamond laboratories, Expt. No. TIG-7; Acc. No. 072022.

Studies on Chronic Toxicity of Injectable Tiquvon in Dogs by C.J. Welter and D.R. Johnson, Diamond Laboratories, Expt. No. TIG-6; Acc. No. 072022.

Determination of Subacute Toxicity and Anthelmintic Efficacy of Injectable Tiquvon in Cats by C.J. Welter and D.R. Johnson, Diamond Laboratories, Expt. No. TIG-10; Acc. No. 072022.

A Tumorigenic Study of Fenthion in Mice by I. Rosenblum, Albany Medical College, 12-80; Acc. No. 072022.

S 1752 Evaluation for Embryotoxic and Teratogenic Effects in Orally Dosed Rats by L. Machemer, Bayer AG Institut fur Toxikologie, Rept. No. 7580, 6-7-78; Acc. No. 072022.

[redacted]

S 1752 Salmonella/Microsome Test for Detection of Point-Mutagenic Effects by B. Herbold, Bayer AG Institut fur Toxikologie, Rept. No. 9088, 4-16-80; Acc. No. 072022.

Fenthion Mutagenicity Test on Bacterial Systems by H. Imukai and A. Iyatomi, Nitokuno Agricultural Chemicals Institute, Rept. No. 30, 7-1-76; Acc. No. 072022.

Report of The Mutagenicity Study of Fenthion by Y. Shirasu, M. Moriya ard Y. Kaneda, Institute of Environmental Toxicology, 1-25-79; Acc. No. 072022.

Ames Test for Lebaycid (Fenthion) by F. Oesch, Mainz, 10-25-77; Acc. No. 072022.

Neurotoxicity Studies on Hens (BAY 29493) Histopathology by W. Diekmann, Bayer AG Institut fur Pathol. Histologie, Rept. No. 2735, April 29, 1971; Acc. No. 072022.

Neurotoxic Studies with BAY 29493 by G. Kimmerle, BAYER AG Institut fur Toxikologie, 5-20-65; Acc. No. 072022.

A Safety Evaluation of Fention (S 1752 in Rhesus Monkeys (Macca mulatta) by I. Rosenblum, Albany Medical College, N.Y., March 1980; Acc. No. 072022.

Tiguvon Pour-On 2% - Incident in Man, Petone, New Zealand (Author Unknown), 3-23-71; Acc. No. 072022.

Safety Evaluation of Fenthion in Human Volunteers by F. Coulson, T. Griffin and I. Rosenblum, Albany Medical College, New York, 6-21-79; Acc. No. 072022.

The following reports are either scientific articles publications or abstracts which contain no detailed or raw toxicity data that are necessary for an adequate toxicological evaluation:

Acute Toxicity Data for Pesticides (1964) by E.F. Edson, D.M. Sanderson and D.N. Noakes, World Review of Pest Control Spring 1965 Vol. 4 Part 1: 36-41.

Poisoning by an Organophosphorus Compound: A Case Report by G. Dean, J. Coxon, and D. Brereton, S.A. Medical Journal, 10-21-67, pp. 1017-1019.

The Action of Reactivators in Phosphoric Acid Ester Poisoning by D. Lorke and G. Kimmerle, Naunyn-Schmiedebergs Arch. Pharmak. exp. Path. 263(1):237 (1969).

Comparative Inhibition of Aliesterases and Cholinesterase in Rats Fed Eighteen Organophosphorus Insecticides by M.Q. Su, F.K. Kinoshita, J.P. Frawley and K.P. DuBois, Toxicol. Appl. Pharmacol. 20: 241-249 (1971).

Toxicological Aspects of Three Organophosphorus Compounds (Cythioate, Famphur, and Fenthion) in the Host-Ectoparasite System by H.G. Smith and R.L. Goulding. J. Economic Entomol. 63(5): 1640-1646 (1970).

Pesticide Residues in Food: 1980 Evaluations. FAO Plant Production and Protection Paper, 26 Sup., pp. 218-234 (1981).

Teratogenicity and Embryotoxicity of Demeton and Fenthion in CF#1 Mouse Embryos by C.H. Budreau and R.P. Singh. Toxicol. Appl. Pharmacol. 24:324-332 (1973).

Mutagenicity Screening of Pesticides in the microbial System by Y. Shirasu, M. Moriya, K. Kato, A. Furuhashi and T. Kada. Mutation Research 40:19-30 (1976).

The Mutagenic Effect of Pesticides on Escherichia Coli WP2 try- by Zs. Nagy, I. Mile and F. Antoni, Acta Microbiol. Acad. Sci. Hung. 22:309-314 (1975).

Delayed Neurotoxicity of Organophosphorus Compounds and Copper Concentration in the Serum of Hens by G. Kimmerle and E. Loser in EQS Environmental Quality and Safety: Chemistry, Toxicology and Technology, Academic Press, 3:173-178 (1974).

BAY 29493 Chronic Toxicity Study on Rats by E. Bomhard (1977) is listed in the "Table of Contents" under "Index Tab 3.5.2b. Actually, this study is absent from this compilation. Instead, an unrelated paper entitled "Beatitude Through Application of Latitude" by H. Frehse and G. Timme (1978) was inserted in its place.

Data gaps exist for a reproduction study, a teratology study in rats, oncogenicity studies in mice and rats, and a long-term non-rodent feeding study.

Existing Tolerances:

Published tolerances of 0.1 ppm Fenthion for cattle, hogs, poultry and rice, and 0.01 ppm for milk and dairy products are listed on the attached computer printout. These tolerances have been established for residues of the insecticide fenthion (O,O-dimethyl O-[4-(methylthio)-m-tolyl] phosphorothioate) and it cholinesterase inhibiting metabolites (40 CFR 180.214).

Acceptable Daily Intake Data:

Toxicity data are insufficient for calculation of an Acceptable Daily Intake (ADI) of fenthion. Therefore, the Maximum Permissable Intake for a 60 Kg human has not been determined.

TMRC

Current	0.0733 mg/day (1.5 kg)
Occupied	0.0255 mg/day (1.5 Kg)
Difference	0.0478 mg/day

The incremental increase of the Theoretical Maximum Residue Contribution (TMRC) from the proposed uses is 0.0478 mg/day (1.5 Kg diet) which is a 187.5% increase.

Conclusion:

Existing toxicity data do not support the proposed uses of the insecticide Fenthion in or on the agricultural commodities grapefruit, oranges and mangoes at 1.0 ppm. Significant data gaps continue to exist as follows:

1. Teratology - A teratology study in a second species, preferably the rat, is required.

2. Reproduction - The multigeneration study in rats which was reviewed in this report did not contain specific raw data necessary for toxicological evaluation. The registrant should submit the raw data, as listed in the review, which may satisfy this requirement.

3. Chronic Toxicity - The 2-year chronic toxicity study in dogs which is reviewed in this report lacked detailed histopathological data necessary for adequate toxicological evaluation. This data should be submitted by the registrant for review.

A 2-year chronic feeding/oncogenicity study is also required in the rat, since the NCI bioassay presented data concerning oncogenic potential without consideration for other chronic effects of fenthion at relatively low doses (10 and 20 ppm). Due consideration should be given to testing at higher doses.

4. Mutagenicity - Representative mutagenicity tests are lacking in two categories: gene mutations and tests for other genotoxic effects. The dominant lethal and micronucleus tests which were reviewed in this report satisfy the requirement for structural chromosome aberration tests.

5. Oncogenicity - An adequate oncogenicity evaluation in the mouse, as well as the rat (listed above under "chronic toxicity").

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CFR 180.214 Pertnior 1/?/..

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ACCEPTABLE DAILY INTAKE [illegible]

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	ADEL	F.F.	TDI	TPI
	mg/kg	UF	mg/Kg/day	mg/day(60kg)
$$$$$$$$$$	$$$$$$$$	$$$$	$$$$$$$$$$	$$$$$$$$$$

Published Tolerances **DRAFT**

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cattle(26)	0.100	7.18	0.01076
Eggs(69)	0.100	3.43	0.00515
Poultry(128)	0.100	2.94	0.00441
Rice(137)	0.100	0.75	0.00083
Milk&Dairy Products(53)	0.010	28.62	0.00429

TPI	TMC	% ADI
$$$$$$$$$$ mg/day(60kg)	0.0255 mg/day(1.5kg)	0.00

****

Current Action 4E2963

Current action not recorded

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Grapefruit(65)	1.000	0.98	0.01457
Oranges(108)	1.000	2.17	0.03250
Tangoes(66)	1.000	0.03	0.00045

TPI	TMC	% ADI
$$$$$$$$$$ mg/day(60kg)	0.7331 mg/day(1.5kg)	0.00

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