UNDATED

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

000997

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE:

SUBJECT: Methoprene Residue Tolerances in/on Peanuts.
PP# 1F2496, Caswell 28AAA, Acc.# 099993, 099994.

FROM: George Z. Ghali, Ph.D. G. Ghali
Toxicology Branch, HED (TS-769)

TO: Gee
Product Manager No. 17
Registration Division (TS-767)

THRU: William Burnam, Acting Branch Chief
Toxicology Branch, HED (TS-769)

Christine F. Chaisson, Section Head C F Chaisson
Toxicology Branch, HED (TS-769)

Registrant: Zoecon Corporation
California Avenue
Palo Alto, California 94304

Action Requested:

Establishment of a tolerance of 1.0 ppm of methoprene residues in/on peanuts and 20 ppm on peanut hulls.

Conclusions and Recommendations:

1. Toxicology Branch recommends for the establishment of the proposed tolerance of 1.0 ppm in/on peanuts and defers to the Residue Chemistry Branch the question of whether food additive tolerances for methoprene residues are required for peanut oil, peanut butter, margarine, and other shortenings.

2. Toxicology Branch recommends for the establishment of the proposed tolerance of 20 ppm on peanut hulls and defers to the Chemistry Residue Branch the question of whether the tolerance existing for methoprene residues in eggs, milk, meat and meat-by-products are adequate to cover the additional use requested.

3. The ADI was previously set on the basis of a NOEL of 1000 ppm (25 mg/kg) from a 90-day rat feeding study and subsequent review of a 2-year rat feeding study.

1812

Recent review of the Tox data for Registration Standard indicated a NOEL of 500 ppm from a 90-day dog study. Taking in consideration the food conversion factor, the dog appear to be the more sensitive species, since on a mg/kg basis the NOEL in the 90-day dog study was considered to be 12.5 mg/kg (500 ppm).

It is therefore concluded that a new PADI based on a NOEL from the 90-day dog study with a 2000 fold safety factor is more appropriate.

4. The registrant is requested to fulfill the Tox data gaps with respect to a longer duration dog feeding study in dog and teratology in mouse.

000997

Existing Tolerances:

There are existing tolerances for methoprene residues (CFR 180.359) as follows:

Cattle	0.30 ppm
Milk & Dairy products	0.05 ppm

Formulations and Use Pattern:

The formulation to be used is "Altosid 5 E", an emulsifiable concentrate, that contains 65.7% methoprene. All inert ingredients are cleared under 40 CFR 180. 1001.

Altosid 5 E will be applied to peanuts by uniform spray as they are transferred to the storage facility, at the rate of 7.6 ounces of formulations per 15 tons of peanuts.

Toxicology Data:

A. Technical Altosid 68.9% a.i.

1. Acute oral toxicity 163.81-1

Rat LD_{50} > 10 gm/kg
Dog LD_{50} > 5 gm/kg

2. Acute dermal toxicity 163.81-2

Rabbit LD_{50} > 3 gm/kg

3. Acute inhalation toxicity 163.81-3

Rat LC_{50} > 210 mg/L/4 hours
Guinea pig LC_{50} 210 mg/L/4 hours

4. Subacute oral toxicity 163.82-1

28-Day feeding-mouse, NOEL 8,000 ppm
28-Day feeding-rat, NOEL 10,000 ppm
14-Day feeding-rat, NOEL 20,000 ppm
14-Day feeding-dog, hypertrophic livers at 5,000 ppm and above.
90-Day feeding-rat, NOEL 1000 ppm
90-Day feeding-dog, NOEL 500 ppm, LEL 5000 ppm (HDT-, increased liver ratios SAP.

5. Subacute dermal toxicity 163.82-1

21-Day dermal-rabbit, NOEL 400 mg/kg/day.

6. Subacute inhalation toxiicty 163.82-4

21-Day inhalation-rat, LC_{50} 20 mg/L/Day (HDT)

7. Oncogenic-Feeding studies 163.83-1,-2

Two-year oncogenic feeding, rat, systmic NOEL 1000 ppm, negative for oncogenicity up to 5000 ppm (HDT).

3

Eighteen-month oncogenic feeding, mouse, systemic NOEL 250 ppm, negative for oncogenicity up to 2500 ppm (HDT), systemic LEL 100 ppm liver pigmentation).

8. Teratogenicity 163.83-3

Rabbits; systemic. reproductive and terata NOEL 500 mg/kg (HDT)

Rat; systemic NOEL 1000 mg/kg (HDT), terata NOEL 500 mg/kg, possible teratogenic effect at 1000 mg/kg (HDT, sternal defects).

Rabbit; systemic NOEL 200 mg/kg, reproductive LEL 200 mg/kg (HDT, embryo lethality in utero), terata NOEL 2000 mg/kg (HDT).

Mouse; additional data are required.

9. Reproduction 163.83-4

Three generation reproduction- rat, NOEL 2500 ppm (HDT).

10. Mutagenicity 163.84-1 thru-4

A dominant lethal study and bacterial testing indicated that methoprene is not mutagenic in these tests.

11. Metabolism 163.85-1

The metabolism of methoprene was investigated in the rat, mouse, quinea pig, steer, and cow. Methoprene is extensively biotranstormed and its carbon atoms are utilized in the biosynthesis of steroids.

B. Altosid 5 E:

The following studies were submitted in support of the current petition: (See review on the next pages)

1. Acute oral toxicity 163.81-1

Rat LD_{50} > 5,000 mg/kg (HDT)

2. Acute dermal toxicity 163.81-2

Rabbit LD_{50}> 20,000 mg/kg (HDT)
caused dermal necrosis.

3. Acute inhalation toxicity 163.81-3

Rat LD_{50} > 4.5 mg/L (HDT)

4. Primary eye irritation 163.81-4

No corneal opacity, slightly irritating, reversible in 7 days. Tox Category III.

5. Primary skin irritation 163.81-4

Not irritating

000997

Review

Acute Oral Toxicity

Test Chemical:

Altosid 5 E, Lot No. FZ 515876

Testing Laboratory:

Elars Bioresearch Laboratories. Project No. 1438-D, February 7, 1979.

Procedure:

Five male and five female young adult Wistar rats provided by Charles River Laboratory were acclimated for one week. Animals were starved for 17 hours prior to dosing with a single dose of 5 gm/kg by gavage. Animals were observed for pharmacological signs and mortality at one, four, and six hours after dosing and daily thereafter for 14 days. All animals were sacrificed and a terminal body weight was taken.

Results:

No death, toxic signs, abnormal food or water intake were observed. Gross pathological examinations revealed no treatment related effects.

Conclusion:

Under the test conditions the oral LD_{50} of Altosid 5 E is >5g/kg.

Core-Classification:

Core-minimum

5

Acute Dermal Toxicity

Tert Chemcial:

Altosid 5 E, lot No. F2515876

Testing Laboratory:

Elars Bioresearch Laboratories. ProjectNo. 1551; May 27, 1980.

Procedure:

Eighteen adult new Zealand white rabbits, nine males and nine females (2-4 kg) were provided by Stevinson Rabbitary, California and acclimated for one week. About 40% of the total skin of each animal was shaved a day before application of the test chemical. The application site was abraded before the application of a single dose of the test chemical at 20 gm/kg by the mean of gauze sponge backed with plastic wrap which were taped to the shaved ventral area with porous adhesive tape. The entire trunk was wrapped with elastic tape. Ten animals were treated with the test chemical and eight animals were used as controls. The test chemical remained in contact with the skin for 24 hours and toxic and behavioral reactions were observed. At the end of 24 hours the bandaging was removed and the skin wiped to remove excess test material. The animals were observed for 14 days for behavioral and toxic reactions. Initial, one week and terminal weights were recorded. All animals which succumbed during the study were subjected to gross necropsy. On day 14 all survivors were killed and subjected to gross necreopsy.

Results

During the 14 days observation period, dermal necrosis, purulent discharge, and alopecia were noted at the Altosid 5 E test areas.

Three test rabbits did not survive the 14 day observation period. One rabbit died on day 10. The examination revealed a scarred area on the chin and dry flaky skin at the test site, and no other lesion at necropsy. The other two rabbits were euthanatized for human reasons on day 6 and 11. Necropsy examination was indicative of both infection and starvation in addition to other pathological symptoms. A third test rabbit exhibited a head tilt and developed a pattern of circling. Two control rabbits were euthanatized during the study. One of them was killed on the first day after breaking its back fighting the wrap. The second was anorexic and lethargic on day 9.

Gross necropsy of animals survived for the duration of the experiment revealed slightly congestd, pale, mottled kidneys and liver tapeworm cysts in test and control animals.

In general most test animals showed body weight loss. the food and water consumption data were not reported to further evaluate this effect. All test animals exhibited skin efects characterized by acanthosis, hyperkeratosis, acute and chronic inflamation, parakeratosis, and ulceration.

Conclusion:

The test material, Altosid 5 E, caused dermal necrosis but no obvious signs of systemic toxicity. The dermal LD_{50} for Altosid 5 E is greater than 20,000 mg/kg.

Core-Classification:

Core-Minimum.

Acute Inhalation Toxicity

Test Chemcial:

Altoside 5 E, Lot No. FZ 515876

Procedure:

Two groups of ten young adult Sprague-Dawley rats(5 males and 5 females), obtained from Charles River laboratories were used. Each group was housed in an inhalation chamber (400L), while individually retained in stainless steel wire mesh compartments. Animals were deprived from food and water during the time of exposure.

Airflow rate through each chamber were determined hourly and maintained at 45 liters/minute and the magnitude of the negative pressure within the chamber was always less than 0.5 inches of water. The temperature and the relative humidity were also measured at hourly intervals.

Both groups were treated concurrently with either the control or test material for a single period of four hours. An hourly air sample was withdrawn from the test chamber for chemical determination of methoprene content. The particle size were also monitored.

After exposure, animals were noted for any signs of toxicity for 14 days. Body weight was recorded on the treatment day and on days 2,3,4,7 and 14 after treatment.

A complete gross pathological examination was conducted on all animals sacrificed at the end of the 14-days observation period. Lungs, liver, kidneys and other tissues that appeared abnormal were histopathologically examined.

Results

All animals in both the control and treatment groups were normal during the exposure period and throughout the boservation period, with rspect to body weight changes and gross and histopathological examinations.

Conclusion:

Acute whole-body inhalation exposure of albino rats to altosid 5 E at a concentration of 4.5 mg/L produced no abnormal clinical, gross or histopathological effects.

7

Core Classification:

Core-Minimum

Primary Skin Irritation

Test Chemical:

Altosid 5 E, Lot No. FZ 515876

Testing Laboratory:

Elars Bioresearch Laboratories. Project No. 1438A, February 7, 1979.

Procedure:

Six young adult (approximately four month) New Zealand White rabbits, obtained from Pel-Freeze Farms, Inc. were used in this experiment.

The animals were allowed to acclimate two weeks. Five hours prior to initiation of the treatment the rabbits were examined and clipped free of hair in the area extending from the shoulders to the hips and halfway to either side of the thorax.

There were four test sites per animal (right and left shoulder, and right and left flank). On the test day, the test areas over th right shoulder and the left flank of each rabbit were abraded. A dose of test chemical equal to 0.5 ml was applied to each of two one-inch square gauze patches backed by Saran Wrap. The patches were applied to the four test sites of each rabbit and secured with porous adhesive tapes and the whole trunk was then wrapped with conform elastic tape. The test material was kept in contact with the animal skin for 24 hours after which the excess test matrial was wiped with gauze sponge. At 24 and 72 hours post treatment, animals were observed and signs of erythema and edema were scored according to Draize.

Results:

At the 24 and 72 hours examinations, no animals showed any signs of irritation. At 5 days after application, some skin craking and flaking off were observed on some treated rabbits. At two weeks sites had cleared up except for some very minor flaking. No erythema was noted during the entire period.

Conclusion:

The test material can be considered non-irritating since the primary skin irritation index average was zero. Skin irritation index less then 0.5 is considered non-irritating.

Core Classification:

Core-Minimum

000997

Primary Eye Irritation

Test Chemical:

Altosid 5 E, Lot No. F2 515876

Testing Laboratory:

Elars Bioresearch Laboratories, Project No. 1438-C, February 21, 1979.

Procedure:

Nine young adult New Zealand white rabbits (4 male and 5 females), obtained from Pel-Freez Farms were used in this study. A dose of 0.1 ml of undiluted test material was placed on the everted lower lid of the right eye of each rabbit. The lids were gently held together for 30 seconds to prevent loss of the test material. The test eyes of six rabbits were then flushed for one minute with warm water. the untreated left eye of each rabbit served as a control. Scoring was made according to Draiz (1959). Three more rabbits were treated on February 24, 1979.

Results:

Rabbits showed slight redness of the conjunctivae, swelling of the conjunctivae in some other, or slight discharge at 24 hours. No corneal opacity was observed except for the three rabbits that were added to the experiment later. this corneal opacity was reversible in 7 days.

Conclusion:

The chemical can be assigned to Tox. Category II.

Core Classification:

Core-Minimum

000997

Primary Eye Irritation

Retesting

Objective of Retesting:

This study was conducted to re-test potential ocular irritation of Altosid 5 E because of suspected contamination of the first sample.

Procedure:

The same procedure and same number of animals were used except that the test material was placed in the left eye instead of the right eye. Only three animals (one male and two females) had their eyes washed with distilled warm water. The same method of scoring was used.

Results:

No corneal opacity. Other symptoms observed such as slight redness of conjunctiva and slight discharge were all reversible by 7 days.

Conclusion:

According to the results of the second test, the chemical can be assigned to Tox Category III.

Core Classification:

Core-Minimum

10

000997

old NOEL change not recorded

CFR 180.359 Methoprene 9/22/81

File last updated 9/22/81

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	PPM	S.F.	ADI mg/kg/day	TPI mg/day(60kg)
50.000	1000.00	100	0.5000	30.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cattle(26)	0.300	7.16	0.03233
Milk&Dairy Products(93)	0.050	28.62	0.02146

TRI	THRC	% ADI
30.0000 mg/day(60kg)	0.0537 mg/day(1.5kg)	0.18

****

Current Action PP# 1F2496

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Peanuts(115)	1.000	0.56	0.00537

TRI	THRC	% ADI
30.0000 mg/day(60kg)	0.0592 mg/day(1.5kg)	0.20

****

11

000997

CFR 180.359 Methoprene 9/22/81

File last updated 9/22/81

ACCEPTABLE DAILY INTAKE DATA

Dog	NOEL	S.F.	ADI	DPI
mg/kg	ppm		mg/kg/day	mg/day(60kg)
12.500	500.00	2000	0.0063	0.3750

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cattle(26)	0.300	7.18	0.03233
Milk&Dairy Products(93)	0.050	28.62	0.02146

DPI	THEC	% ADI
0.3750 mg/day(60kg)	0.0538 mg/day(1.5kg)	14.34

****

Current Action PP# 1F2496

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Peanuts(115)	1.00	0.36	0.00537

DPI	THEC	% ADI
0.3750 mg/day(60kg)	0.0592 mg/day(1.5kg)	15.78

****