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TAR-356

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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DATE: April 25, 1979

SUBJECT: Kabat or Isopropyl (E,E)-11 methoxy-3,7,11-trimethyl-2,4-dodecadienoate - Application for registration #20954-RI sprayed on tobacco at 10 ppm before placing tobacco in hogshead for storage.

FROM: Salvatore Biscardi, Pharmacologist
TOX/HED TS-769

TO: Mr. Franklin Gee
PM-17

THRU: Dr. A. Gross
Chief, Toxicology Branch
TOX/HED

Company: Zoecon Corporation
975 California Ave.
Palo Alto, California 94304

Synonyms: Kabat (IGR)
Methoprene
Altosid
ZR-515
EMT 70460

Conclusion to the Request for Registration

The four fold safety factor between the calculated exposure of man to 2.30 µg/kg/day to the maximum exposure of 9.6 µg/kg/day in the rat experiment must be considered the least safety factor and not the actual safety factor since no toxicity in the rat was attributable to methoprene administration.

It would appear therefore that the use of methoprene in cigarette tobacco at the concentration of 10 ppm can be toxicologically supported by the evidence submitted.

Chemical Identity, Altosid Technical

A. Chemical Name - Isopropyl (E,E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate

B. Chemical Abstracts Name and Registry Number - The Chemical Abstracts Service (CAS) systematic name for methoprene is:

2,4-Dodecadienoic acid, 11-methoxy-3,7,11-trimethyl-, 1-methylethyl ester, (E,E)-

The CAS Registry Number is 40596-69-8.

EPA FORM 1320-6 (REV. 3-76)

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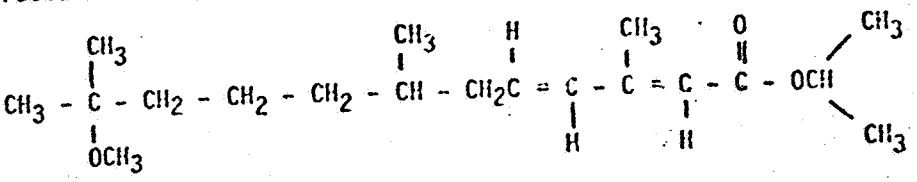
C. Empirical Formula: $C_{19}H_{30}O_3$

D. Structural Formula:



E. Molecular Weight: 310

Physical and Chemical Properties - Altosid Technical

A. Physical Properties

State or Form:	Liquid
Color:	Pale Yellow
Odor:	Faint Fruity Odor
Boiling Point:	100°C at 0.05 mmHg
Vapor Pressure:	2.37×10^{-5} mmHg at 25°C
	1.60×10^{-4} mmHg at 40°C
Solubility:	All organic solvents - Infinite Water - 1.39 ppm
Specific Gravity:	0.9261 gm/cc at 20°C
Flash Point:	370°F - Open cup method

B. Spectral Data - Altosid

Confidential Statement of Formula

	% by Wt
[redacted]	

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Title: Subacute Inhalation Study in Rats

Project. 777-125

Testing Lab: Hazelton Laboratories of America Inc.

Sponsor: Zoecon Corporation

Date of Repo.t: July 21, 1978

Test Compound: Methoprene

Test Specie: Rat, Sprague-Dawley

Number of Animals: 60 (175-280 grams each)

Route of Administration. Inhalation

Dose and Duration of Exposure: Four hour periods - (16 cigarettes)
5 days/wk - 6 weeks

Methodology:

The animals were exposed to smoke from cigarettes puffed once per minute for nine puffs each. Each 35 ml puff is drawn in 2 seconds into the inhalation chamber and dispersed throughout the chamber by a 2 second burst of air set at 50 liters/minute. The chamber air now remains static for 20 seconds then purged for 36 seconds using airflow at 50 liters per minute. A 5 minute period of purging using 50 liters/minute takes place between each cigarette.

Animals were otherwise kept in hanging mesh cages, 40 sq. in/cage. Tap water and food was at libitum. Samples of smoke were taken for analysis. A substudy was performed in rats to determine whether the rats were actually inhaling smoke. This was established by measuring plasma nicotine.

Dosage levels were:

Group I - control - no methoprene

Group II - 72 µg/gram

Group III - 308 µg/gram

Cigarettes were filter tipped.

Body weights, clinical signs and survival, hematology, clinical chemistry and terminal studies were undertaken including gross and histopathology on:

brain	liver	stomach
thyroid	kidney	small and large intestine
trachea	larynx	gonads
lungs	spleen	peripheral nerve
heart	adrenal	skeletal muscle

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and histopathology on:

brain	heart	gonads
thyroid	liver	larynx
trachea	kidney	nasal turbinates
lungs	adrenal	

Statistical analysis on the data was performed.

Results

Chamber CO concentrations varied between 60 and 80 ppm with range from 30 to 110 ppm.

Plasma nicotine showed animals were inhaling smoke in the inhalation chamber and were therefore being challenged by the cigarette smoke.

Body weights varied between groups as not to indicate a consistent methoprene related weight effect. The anorexigenic activity of tobacco smoke is well known.

Clinical chemistry values varied between groups. Of significance, at first glance would be the elevated blood sugar levels in both males and females.

Males had 91 ± 16 mg/dl in controls, 115 ± 15.7 mg/dl at the low dose level and 135 ± 25 mg/dl at the higher dose level.

Females had 111 ± 13.6 mg/dl in controls, 134 ± 22.9 at the low dose level and 141 ± 33.8 at the high dose level.

The increase in blood sugar may be attributed to the increased amount of [redacted] for the methoprene. This [redacted] is not present in the control cigarettes. It is known that nicotine produces an increase in circulating catecholamines including epinephrine[1]. Epinephrine, in turn, is known to produce an increase in circulating blood sugar and free fatty acids.

Gross Pathology showed a high incidence of thickening of the nasal turbinates and enlarged peribronchial lymph nodes but in all groups including controls. This effect, therefore, should be attributed to the smoke factor alone.

Lung weights were higher in treated male rats but not in treated females. This effect may not be methoprene related.

Conclusion to the study

The toxicity of tobacco smoke, the toxicity due to the vehicle used to prepare the experimental cigarettes [redacted] would make it difficult to assess the added toxicity that may be attributed to methoprene. But since there is little or no toxicity that can be observed to begin with except for the effects on the upper respiratory system including control animals, it may be assumed that methoprene does not have a toxic effect in rats exposed according to the above schedule and concentrations.

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1 A Manual of Pharmacology - by T. Sollman, M.D. - pg 454

Rat Exposure to Methoprene

According to Dr. Coate, the methoprene concentration over the 10 minute course of smoking one cigarette was 4.0×10^{-5} µg/cc. The rat is exposed to 60 sec/min for nine puffs per cigarette or 540 seconds plus an additional 60 seconds to fully purge the chamber of smoke between cigarettes for a total of 600 breaths. The tidal volume of rat is 1.5 ml on the basis of a 300 gram rat,and 16 cigarettes/day, actual exposure would be

4.0×10^{-5} µg/cc x 1.5 cc x 600 breaths x 16 cigarettes ÷ 0.3 kg =

1.92 µg/kg /day for the low dose cigarette and 9.6 µg/kg/day for the

high dose cigarette.

Human Exposure

The smoker (2 packs per day) weighing 45 kg (woman body weight) would be exposed to:

1.61 µg/cigarette x 40 cigarettes ÷ 45 or 1.43 µg/kg body weight/day

The 1.61 µg/cigarette dose is calculated from 10 ppm or 10 µg sprayed on tobacco. Only 90% of each cigarette is composed of treated tobacco. Eight percent of each cigarette is smoked. Sixty-two percent of methoprene particulates pass through the filter and thirty-six percent of applied methoprene appears in mainstream smoke or

(10 µg) (90%) (80%) (62%) (36%) = 1.61 µg/cigarette

It was later learned that the cigarettes used in the experiment were filtered cigarettes. The correction factor for the nonfiltered cigarettes raises the amount of methoprene exposure from 1.43 µg/kg/day to 2.30 µg/kg/day. This represents an exposure of about one-fourth of the maximum rat exposure or a four fold safety factor.

A subsequent letter dated March 30, 1979 states that these calculations are conservative because now only 30% of the tobacco in each cigarette will be methoprene treated instead of the 90% as previously stated.

In addition Zoecon Corporation claims that 87% of the smokers use filtered cigarettes and that the average smoker consumes 27.4 cigarettes per day rather than the 40 cigarettes per day as in the extreme case used in the calculations. There is also a diminution of 20% of methoprene after two years storage of treated tobacco which was not accounted for in the calculations.

This reviewer adds that the amount of methoprene entering the mouth does not correspond to the amount of methoprene reaching the actual respiratory apparatus (alveoli) of the lung in the human. Condensation of methoprene will take place on the mucosa of the mouth, and upper digestive tract which is common with the mucosa of the upper respiratory tract. Oral ingestion of methoprene from tobacco smoke is therefore another consideration that diminishes still further the amount of methoprene which enters the larynx and trachea. More methoprene (an amount difficult to assess) will still condense on the

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respiratory cilia whose function is to remove condensates up and out of the trachea. Any amount of methoprene which will reach the alveoli will be so small as not to present a toxicological problem incrementally significant above the toxicity induced by untreated tobacco smoke per se as can be assessed by the rat exposure data. It is to be noted moreover that the column of air traveling from the nose of the rat to the alveoli is many times shorter in the rat than in man.

The miniscule amount of methoprene absorbed systemically from the oral route would not present a toxicological problem as the additional studies have already shown in consideration of past tolerances for methoprene.

Methoprene tolerances

While tobacco is not considered a food, toxicological considerations for methoprene have already permitted tolerances for residues on cattle, fat at 0.3 ppm and on milk at 0.05 ppm according to 42 FR 22365 of May 3, 1977 Section 180.359. (See attachment 1)

[redacted]

Label

A revised label was submitted 3/23/79 in keeping with Toxicology Branch's concerns regarding eye and skin irritation potential of Kabat formulated [redacted]. The signal word is now WARNING and the formulation now falls within EPA toxicity category II.

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