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CIBA-GEIGY

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10/11  
(52)

January 22, 1986

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

SANITIZED

Document Control Officer  
Chemical Information Division  
Office of Toxic Substances (WH-557)  
Environmental Protection Agency  
401 M Street, S. W.  
Washington, DC 20460

8EHQ-0186-05855

88-8600058

Initial

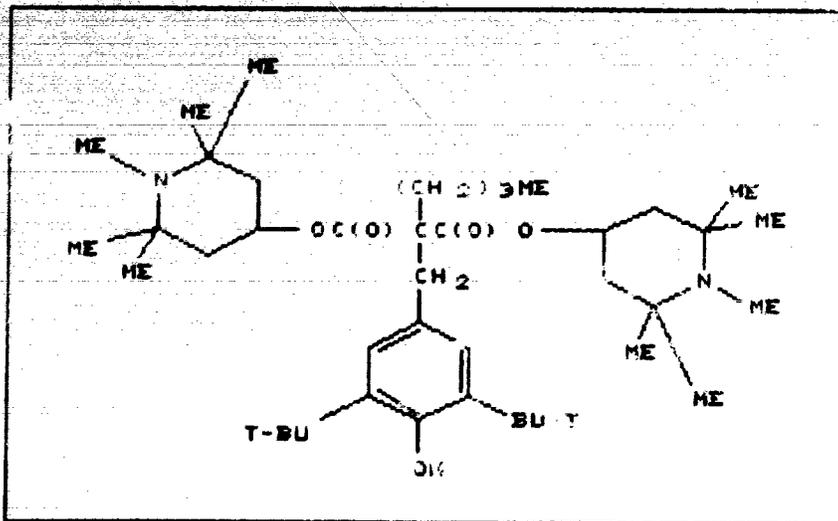
Re: Potential TSCA Section 8(e) Notice

Dear Madam or Sir:

CIBA-GEIGY Corporation requests that the production volume shown in brackets in this letter be treated as Confidential Business Information. We enclose a sanitized copy of this letter for the public file.

Pursuant to Section 8(e) of the Toxic Substances Control Act, CIBA-GEIGY Corporation is submitting results of a 28-day study in rats with Tinuvin 144 to request the Agency's advice on whether the findings of an apparent immunosuppressive effect in such a study is subject to a mandatory reporting obligation. This study has been recently reviewed for the first time by a CIBA-GEIGY Corporation toxicologist in connection with OSHA's Hazard Communication Standard (29 CFR 1910.1200).

Tinuvin 144 is an ultraviolet light stabilizer used in automobile coatings and polypropylene fibers. Chemically, it is Propanedioic acid ((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)methyl)butyl-bis(1,2,2,6,6-pentamethyl-4-piperidinyl)ester (CAS No. 63843-89-0), with the following structure:



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The product is an off-white crystalline powder, having a melting point of 146-150°C and a vapor pressure of approximately  $1 \times 10^{-10}$  mm Hg at 20°C. Its molecular weight is 685. Current annual sales are approximately [ ]

Although we are enclosing a full copy of the 28-day study entitled, "Preparation BK-11927, Report on the 28-Day Toxicity Study, Oral Administration - Rat," the results may be summarized as follows:

Rats received daily gavage doses of 0, 60, 100, 300, 600 and 1000 mg/kg. for 28 days. The corresponding mortality rates for these respective groups were as follows: 0, 0, 30, 70, 80 and 100%. Where observations could be made, all dose levels produced alterations in white blood cell parameters and thymus weight as well as lesions in the spleen, abdominal lymph nodes, and liver.

The lesions were described as abscesses which occurred in 5 of 10 animals at 100 mg/kg and in 2 of 10 animals at 60 mg/kg. In addition to these lesions, there was a significant dose-related decrease in thymus weight and thymic tissue atrophy. The decrease in the weight of the thymus for males was 42%, 56% and 94% in the 60, 100 and 300 mg/kg groups, respectively. Females showed decreases of 10%, 46%, and 91% in the corresponding dose group. Significant changes in the white blood cell parameters included marked elevations in the number of leukocytes and segmented neutrophils, as well as dramatic reductions in the number of lymphocytes.

Aside from the question of whether this information is 8(e) reportable, which we request the Agency to address, CIBA-GEIGY Corporation does not believe the reported effects present a substantial risk of injury to human health for the following reasons:

- a) Workplace exposure to Tinuvin 144 is generally limited to initial manual transfer operations. Subsequent mixing and master batch production operations are carried out mechanically in large scale mixing equipment.
- b) The product is flowable and particles adhere to one another. Manual transfer operations thus produce minimal dusting.
- c) The moderately high molecular weight and limited water solubility should significantly reduce skin penetration.
- d) The five major customers using this product are health and safety conscious and already employ protective equipment to reduce exposure to solvents and other hazardous chemicals used in the same operations. One customer requires "space suits" to be worn when handling the product (because of other chemicals used).
- e) Once formulated into polypropylene masterbatches, exposure to Tinuvin 144 is precluded as the polyolefin pellets are generally 1/16 - 1/8" in diameter. User exposure further downstream is also largely precluded since the product is encapsulated within the plastic substrate.

- 1) In automotive coatings, Tinuvin 144 is completely enclosed in the dried vehicle of the coating system.

We concluded, however, that even if this does not represent a substantial risk, EPA may want this type of information since other uses in the future might involve greater exposure.

To further reduce any risk to CIBA-GEIGY workers and downstream users, the company has done the following:

1. Revised its Material Safety Data Sheet to reflect the subject findings (copy enclosed).
2. Revised its label (copy enclosed) to read in part....

"NOTICE: Liver, lymphoid, and blood system effects were seen in a feeding study conducted in laboratory animals. The relevance of these findings to humans is unknown."

In accordance with the OSHA Hazard Communication Standard (29 CFR 1910.1200), our customers will be notified of these findings via the revised MSDS and label within 90 days. CIBA-GEIGY workers will be informed via the revised MSDS and the company's OSHA Hazard Communications Program.

Please contact me if you have any questions or want additional information.

Very truly yours,

*A. Di Battista*

Anthony Di Battista  
Manager, Toxic Substances Compliance  
Safety, Health & Ecology

ARB17-88:36  
Enc.

LABEL PA-A 55

For: Tinuvin 144

Tinuvin 144 FLD

Read Material Safety Data Sheet Before Handling.

NOTICE! Liver, lymphoid, and blood system effects were seen in a feeding study conducted in laboratory animals. The relevance of these findings to humans is unknown.

May cause skin, eye, and respiratory tract irritation.

Avoid swallowing. Avoid inhaling dust. Avoid eye contact and repeated or prolonged skin contact. Wear chemical goggles and impervious gloves as standard handling precautions. Wear a NIOSH approved dust mask or respirator as required. Wash thoroughly after handling. Use with adequate ventilation. Keep container tightly closed when not in use and during transport.

First Aid, in case of contact:

Eyes: Flush eyes with plenty of water for at least 15 minutes. Get medical attention.

Skin: Wash with mild soap and plenty of water.

Inhalation: Remove to fresh air.

Ingestion: If conscious, give plenty of water, and induce vomiting. Get medical attention.

Clothing: Remove contaminated clothing and wash before reuse.

For Industrial Use Only.

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CIBA-GEIGY LIMITED  
Pharmaceuticals Division  
Toxicology / Pathology

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LABORATORY REPORT

(CAS No. 63843-89-0)

PREPARATION TK 11 927

TINUVIN 144

REPORT ON THE 28-DAY TOXICITY STUDY

ORAL ADMINISTRATION - RAT

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TK 11 927

Exp. No.: 7608302

S U M M A R Y

Preparation TK 11 927 was subjected to a 28 day toxicity study in rats. The test preparation TK 11 927 was administered orally by gavage once daily, seven days a week at daily doses of 60, 100, 300, 600 and 1000 mg/kg. Each dose group as well as the control group which had received only the suspension medium consisted of 5 male and 5 female albino rats. Mortalities and symptoms were registered daily, body weight gain 3 times and food consumption once weekly. Laboratory investigations were performed at the end of the experiment and also earlier in those animals - except the females of the 600 mg/kg/day-group - which had to be sacrificed due to poor general condition in the course of the experiment.

All rats of the 1000 mg/kg/day-group died between day 3 and 6. Five male and 3 female rats of the 600 mg/kg/day-group died between day 4 and 7. Two females of this group had to be sacrificed due to poor general health on day 7. Four male and 3 female animals of the 300 mg/kg-group succumbed between day 5 and 10. The remaining rats (1 male and 2 females) had to be sacrificed because of poor general condition. Three female rats of the 100 mg/kg-group died between day 11 and 27. No mortalities occurred after 60 mg/kg/day.

The main symptoms observed in all dosed group - except the 60 mg/kg-group - were muscular hypotonia, rough coat, ataxia, meteorism, ptotic eye lids and kyphotic carriage. The 1000, 600 and 300 mg/kg-group showed also diarrhea, brownish eye discharge, stiff movements and, only the 1000 and 600 mg/kg-groups, soiled snout. Respiration was slower in the top dose group.

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Loss of body weight was observed in the animals of the 1600, 600 and 300 mg/kg-groups. Delayed development in the animals of the 100 mg/kg-group was observed. After 60 mg/kg body weight gain was not impaired in female rats while the males showed weight loss from day 21 onwards.

Food consumption was low in all dosed groups except in the 60 mg/kg females.

The males of the latter showed lowered food intake during week 4. Laboratory investigations performed in 1 male and 2 females of the 300 mg/kg-group on day 11 revealed low potassium, low glucose levels and an increase of BUN and GPT. An increase of hemoglobine content, of erythrocytes and of packed cell volume indicative for dehydration caused by diarrhea and marked leucocytosis was observed in these rats. The differential blood count showed that the latter was caused by marked increase of neutrophilic cells and that there was a relative lymphopenia. These rats showed also a marked prolongation of prothrombine time.

The 100 mg/kg-group revealed an increase of GPT and GOT and a decrease of proteins. The albumine fraction of the electropherogram showed a decrease while the  $\alpha_1$ - and  $\Sigma\beta$  globulin fractions were increased. Haemaocrit values were found to be decreased and the number of leucocytes to be increased. There was a relative decrease of lymphocytes and an increase of neutrophils in the differential blood count.

After 60 mg/kg/day a slight but significant increase of leucocytes caused by an increase of neutrophilic cells was noted at the end of the study. There was also a relative lymphopenia shown in the differential blood count.

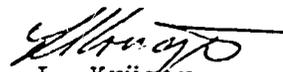
The data of all other parameters investigated were found to be within physiological limits valid for the strain of rats used.

At the end of the study the animals were referred to pathology and autopsied. Special attention was paid to the sympathetic nervous system and ganglia. In the latter transmitter function was checked in some rats by histochemical techniques.

Nearly in all rats treated with 60 mg/kg and 100 mg/kg of TK 11 927 (which survived until the end of the experiment) increased amount of neutrophilic and eosinophilic leucocytes in the lungs and marked accumulation of large foamy cells in the mucous membrane of the small intestine, in enlarged abdominal lymph nodes and in the spleen were seen at histological examination. Abscesses in the liver, spleen and abdominal lymph nodes were found in two rats from the 60 mg/kg-group and in 5 rats from the 100 mg/kg-group. Mucosal erosions and superficial gastric ulcers occurred in 6 rats from the 100 mg/kg-group.

In rats from the 300, 600 and 1000 mg/kg-dosage groups (which died or were sacrificed during the test period) atrophy of the thymic tissue and in males animals also impaired spermatogenesis were observed.

The qualitative and quantitative neurohistochemical examination (see separate report) of the noradrenaline content of neurons in the iris, the superior cervical ganglion and the vas deferens and the dopamine content of neurons in the striatum did not reveal any difference between treated and control animals.

  
L. Krüger

METHODS

**Species** : rat strain: Lif:RAY<sub>f</sub>(SPF)

**Husbandry** : air-conditioned rooms (temperature: 22±2°C; relative humidity: 50±5%, 16 hours light/day); groups of 5 animals in Macrolon cages (size 3)

**Feed** : pelleted standard diet (Nafag no. 890)

**No. of animals/group** : 5 m and 5 f

**Initial bodyweight** : 98 - 138 g

**Initial age** : 5-6 weeks

**Doses** : 0, 60, 100, 300, 600, 1000 mg/kg daily

**Preparation** : TK 11 927  
daily fresh suspension with 0.5% CMC\*/tap water

**Route of administration** : oral by gavage

**Volume administered** : 10 ml/kg

**Frequency of administration** : daily for 7 days per week

**Duration of administration** : 28 days

**Follow-up period** : -

**Concentration of active ingredient** : 0.6, 1, 3, 6, 10%

**Control group received** : equal volume of 0.5% CMC (Carboxymethyl-cellulose-Na, highly viscous, "Herkules 70 S")

Blood sampling : retrobulbar venous plexus (animals under light ether anaesthesia)

Urine sampling : single oral administration of 25 ml water/kg bodyweight, urine samples of each rat are collected over a 2 hours period in metabolism cages

Euthanasia : exsanguination in ether anaesthesia

Observations and Records

Mortality : daily

Symptoms : daily

Bodyweight : 3 times weekly

Food consumption : weekly

Blood chemistry : on day 28

Haematology : on day 28

Urinalysis : on day 25

Body temperature : -

Eye examination : -

Auditory perception : -

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The animals were referred to pathology on completion of the study (for results see pathology report).