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Office Memorandum • UNITED STATES GOVERNMENT

TO : PESTICIDE BRANCH

DATE: June 25, 1959

FROM : Division of Pharmacology

148130

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SUBJECT: Request for a tolerance for Dodine (dodecylguanidine acetate) on apples, pears, and sour cherries.

Pesticide Petition No. 211

American Cyanamid Co.

The petitioner requests a tolerance of 10 ppm Dodine on apples, pears, and sour cherries, and submits the following data from the American Cyanamid Company Central Medical Department, Industrial Toxicology Section, Stamford, Conn., to support this request.

Acute Toxicity:

A. Rat - For determination of the acute oral LD50, Dodine was administered as a 10% aqueous suspension to young male and female rats (10 per dose) of the CFN strain. The vehicle was a solution of 0.2% agar plus 0.1% "Twcen" 80. The following were the determined LD50's:

LD50's with 95% confidence limits mg/kg

Males, fasted	750 (660-870)
Males, unfasted	870 (705-1030)
Females, unfasted	660 (525-830)

Signs of toxicity following large single doses were not unusual. A steadily increasing degree of depression with diarrhea commencing after 10 to 12 hrs is observed. Death may be delayed two to three days. Post-mortem examination revealed a minor degree of G.I. tract irritation with intestinal contents converted to a clear, yellowish, gelatinous mass. The stomach and portions of the intestine were frequently distended with gas.

B. Mice - Dodine was administered to young male mice (ten per level) as a suspension in aqueous agar. The LD50 and 95% confidence limits are calculated as 1720 (1120-2430) mg/kg.

C. Rabbits - Four groups of male rabbits (4 per group) received single applications on the closely clipped skin of the abdomen. The calculated LD50 was 2.1 (1.5 - 3.0) mg/kg. At gross autopsy the following observations were noted: diffuse subcutaneous hemorrhage, enlargement of the mesenteric lymph nodes and hyperemia of the stomach together with thickening of the pyloric area.

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Dodine - cont.

A quantity of approximately 10 mg of the dry product was introduced into the conjunctival sac of the right eye of each of 5 male albino rabbits. There followed immediate discomfort followed by the development of severe conjunctivitis; at the end of 24 hours the degree of injury was assigned a maximum score 110 according to the scale of weighted scores for grading the severity of ocular lesions used by Draize et al.

A volume of 0.1 ml of the 0.12% aqueous dispersion was introduced into the conjunctival sac of the left eye of each of 5 male albino rabbits. In two cases no irritation occurred. In the remaining three a very slight reddening and swelling of the conjunctivae together with moderate discharge was noted at 4 hours. No sign of irritation remained by 24 hours after application of the dose.

Subacute Toxicity:

A. Rats - CFN rats (19M & 19F on control and 20M & 18F on 3200 ppm Dodine) were fed for 14 weeks. Histopathological examinations were made of 12 rats, 3 of each sex from test and control groups.

All animals survived the 14 weeks. The growth of the males and females receiving 3200 ppm Dodine was immediately and markedly inhibited; these animals had a reduced food consumption. At autopsy neither gross nor microscopic study disclosed any pathology that could be related to ingestion of Dodine.

Chronic Toxicity:

A. Rats - 40 males and 40 females per group were fed 0, 50, 200 and 800 ppm Dodine for two years. 5 animals of each sex per level were sacrificed at 27 and 53 weeks, and 3 animals of each sex per level were sacrificed at 78 weeks. After one year of feeding the rats on the 800 ppm Dodine weighed less and also had a lower food consumption. At the end of two years the animals on 800 ppm Dodine still weighed less than the controls. The males on this level ate slightly less than the controls. Otherwise two year feeding of Dodine to rats demonstrated no specific toxicity grossly or microscopically.

The effect of the feeding of Dodine on reproduction in rats was also studied. 12M and 6F rats from the 800 ppm Dodine and a like number from the controls were mated. The F1 generation (first descendent generation) were weaned on the diets their parents had received and maintained on these for 6 to 12 months. During this time the animals receiving 800 ppm Dodine exhibited the same slight retardation of growth and slightly diminished food intake that was noted in the case of their parents. The F1 generation was

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Dodine - cont.

mated three successive times. The second generation (F2) were destroyed at weaning.

The continuous feeding of 800 ppm Dodine had no significant effect on reproduction and lactation performance of two successive generations of albino rats. Furthermore the animals of the F1 generation maintained on 800 ppm Dodine showed no deleterious effects either grossly or microscopically other than growth inhibition and slight depression of food intake.

B. Dogs - Two male and two female dogs per level were fed the following levels for one year: 0, 50, 200 and 800 ppm. No significant alterations in hemoglobin, hematocrit, total and differential leukocyte counts, blood sugar were observed in any of the test animals in comparison to their controls.

Grossly the thyroid gland of two animals on 800 ppm were somewhat darker in appearance. Microscopically, the only changes attributable to Dodine were observed in the thyroid gland of one animal at 200 ppm and of all four animals at 800 ppm. The thyroid glands of the animals at 800 ppm showed definite stimulation with the very threshold of the effect at 200 ppm.

Therefore the "no effect" dosage level for the one year dog study lies between 50 and 200 ppm. Due to the very slight effect at 200 ppm we can reasonably assume that 100 ppm Dodine fed in the diet for one year would be a "no effect" level in dogs.

Conclusion:

Food Division has stated that with a 7 day pre-harvest interval for apples and pears, the residue will be 5 ppm Dodine. They further state that the residue for sour cherries is 5 ppm Dodine. A tolerance of 5 ppm Dodine for sour cherries, apples, and pears is safe. Since the "no effect" level for dogs, the most susceptible animals used, is approximately 100 ppm Dodine, the establishment of a 5 ppm tolerance in all foods would allow a margin of safety of 20. However, based upon the per capita food consumption figures of the USDA, the use of Dodine on all fruits and vegetables would increase the margin of safety to 77 since fruits and vegetables make up about 26% of the total human food as sold in grocery stores. This margin would increase considerably when allowance is made for discarding the roughage and rinds of fruits and vegetables. Therefore, the establishment of a tolerance of 5 ppm Dodine for apples, pears, and sour cherries will result in the margin of safety being greater than 100.

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*Jane B. McCaulley*  
Jane B. McCaulley  
Div. of Pharmacology

*O. Garth Fitzhugh*  
O. Garth Fitzhugh  
Div. of Pharmacology

OGFitzhugh:hos  
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