Memorandum

2,4-D/Tox (1)

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TO : MR. STOKES
PETITION CONTROL BRANCH

DATE: Dec. 5, 1963

Releasable

FROM : Dr. G. E. Whitmore G. E. Whitmore
Division of Pharmacology, Toxicology Branch

SUBJECT: Isopropyl ester of 2,4-D used as a post-harvest fungicide on lemons. Regarding letter dated July 5, 1963 from J. E. Swift of the University of California, Berkely, California.

Division of Food's data review concluded that the post-harvest use and a combined pre and post-harvest use of isopropyl ester of 2,4-D on lemons would not result in the 5 ppm 2,4-D acid residue tolerance on lemons to be exceeded. They further concluded that similar residues occur from pre, post and combined pre and post-harvest applications of the isopropyl ester of 2,4-D to lemons.

Meat and milk residues are unlikely to occur because commercial practice is such that only untreated lemons would be processed to the pulp stage to become possible cattle feed, according to the Division of Food's review, therefore, safety to animals is not a consideration with this tolerance request.

Division of Pharmacology's chronic toxicity studies of 2,4-D in dogs and rats have demonstrated a no effect level of 500 ppm in the dog-tentatively the same level in the rat, contingent upon a negative histologic report of grossly normal organs at necropsy.

USDI Fish and Wildlife Service Circular No. 167 lists in Table 5A the results of a study on decrease in oyster shell growth as influenced by various pesticides. 2,4-D, 2,4-D dimethylamine salt, and 2,4,5-T acid produced no decrease in oyster shell growth at concentrations of 2 ppm in sea water. 2,4-D butoxyethanol effected 50% growth decrease at 3.75 ppm. In contrast, DDT produced 50% decrease shell growth at a concentration of 0.007-0.009 ppm and lindane produced 43% decrease at 1.0-0.45 ppm concentrations.

A study of levels reported in Circular No. 167 of concentrations of pesticides in sea water resulting in a 50% kill of juvenile white mullet fish recorded no kill with 2,4-D acid at 50 ppm in contrast to DDT killing 50% at 0.0004 ppm and lindane killing 50% at 0.03 ppm. Two esters of 2,4-D-propylene glycol butyl ether ester and butoxyethanol ester killed 50% of longnose kill fish within 48 hours at concentrations of 4.5 and 5.5 ppm, respectively. This is in contrast to a concentration of 0.0055 ppm of DDT and 0.24 ppm of lindane needed to affect a 50% kill in a same time period; 2,4,5-T did not produce deaths at concentration of 50 ppm.

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Studies of effects reported in Circular No. 167 on natural phytoplankton communities during a four hour exposure to a concentration of 1 ppm of 2,4-D acid, 2,4,5-T acid and 2,4-dimethylamine salt revealed no change from normal productivity. In contrast, DDT produced a 77.2% decrease and lindane a 28.5% decrease of productivity of the communities studied.

Table 3D in Circular No. 167 list the effects of three 2,4-D derivatives on reproduction in mallard ducks. The acetamide derivative was apparently without effect at a diet level of 500 ppm. Survival of young was similar in treated and control groups. Number of chicks per hen numbered 10.7 compared to 12.4 per hen for controls. The butoxyethanol ester of 2,4-D fed at 1,000 ppm did not affect survival of young or adults for a 100 day feeding when compared to control birds but only 1.3 chicks per hen were produced.

The dimethyl amine salt of 2,4-D fed to mallard ducks at a diet level of 500 ppm for 100 days did not affect survival of adults but did lower the young survival of 76% in comparison to 89.4% survival of the controls. Five and one tenth per cent chicks per hen were produced on this 500 ppm diet.

These data demonstrate a 500 ppm no effect level of 2,4-D acetamide for mallard ducks and a possibility of a similar level for the butoxyethanol ester. The 500 ppm diet level of the dimethylamine salt has an apparent effect on reproduction and survival in the mallard duck.

Table 2, page 104 of Circular No. 167 lists relative toxicities of commonly used pesticides with DDT equal to one. 2,4-D derivatives are listed as one general group with relative toxicity scored as 0.2-rats, ca. 0.5 bobwhite, ca. 0.5 phesants, ca. 0.5 mallards, and 0.1 for bluegills. 2,4,5-T derivatives are scored as ca. 0.4 rats, 0.2 bobwhite, 0.1 phesants, 0.2 mallards, and 0.1 for bluegills related to the toxicity of DDT expressed as one.

Palmer, 1963 (1) reported a feeding study of 2,4-D alkanolamine salts to cattle given 50 mg/kg on a five day week for approximately 22 weeks (112 doses) as a no effect dosing level.

The 2,4-D data in the Fish and Wildlife Circular No. 167 referred to above and the cattle feeding experiment by Palmer is additional evidence of the low toxicity of 2,4-D and its derivatives. Some of that data can be assessed as reproduction studies of a type, i.e., the no effect level of 500 ppm of acetamide 2,4-D derivatives on fertility and hatching of mallard duck eggs. A comparison to butoxyethanol ester of the acetamide cannot be made since 1,000 ppm was the lowest diet level of the butoxyethanol ester.

The dimethylamine salt of 2,4-D resulted in an apparent drop in ducklings produced per hen to about 1/2 of that produced in those fed acetamide. This may or may not be significant and the raw data are not available for review.

"There is but a slight difference in the toxicity of the free acid and of its salts and ester. The single oral lethal doses for the rat, in mg/kg, body weight, of the sodium salt, and the various esters of 2,4-D are (salt in aqueous, esters in oily solution):

ACUTE ORAL TOXICITY 2,4-D AND DERIVATIVES

mg/kg/b.w.	LD_{50} ORAL RAT
2,4-D acid	300 - 470
Na. salt	610 - 1,060
Isopropyl ester	570 - 860
Mixed butyl esters	320 - 950
Mono, di, tripropylene glycol butyl ether ester	510 - 640

"This group of herbicides also have a low degree of chronic toxicity. 2,4-D and 2,4,5-T can be tolerated without adverse effects in doses only slightly lower than those which cause toxic doses when given in a single dose."

(Garner, R. J., 1961-Veterinary Toxicology, Second Edition, Williams and Wilkins Company, Baltimore, Maryland.)

Available toxicological data very clearly demonstrates a low toxicity of 2,4-D, 2,4-D esters, and salts. Some comparative acid, ester, and salt toxicology have demonstrated similar degrees of toxicities.

CONCLUSIONS:

A mammalian reproduction study has not been presented. This is a necessity if additional residues would be added to the diet of humans by a new use. However, this proposed post-harvest application to lemons of the isopropyl ester would not result in increased residues in the human diet (see DF's memo).

Sufficient toxicological data are available on the acid, esters, and salts of 2,4-D to state that the proposed use change is without undue hazard.

The Division of Pharmacology's chronic toxicity studies of 2,4-D is supportive evidence of this chemical's low toxicity.

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