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Preliminary Review of the Teratology and Selected Toxicology Studies for Captan, Folpet, and Captafol

During the period since World War II, the emphasis on increased food production has stimulated the use and development of fungicides for control of plant diseases. Captan, folpet and captafol were introduced to fit this need. More recently, there has appeared the need to reevaluate toxicology knowledge and use of pesticides in the interest of our environment.

Early toxicology studies with captan and folpet indicated them to be relatively safe to use on agricultural crops. However, the Mrak Report recommended that we minimize human exposure to those pesticides (including captan) considered to present a potential health hazard to man. Captan was one of the compounds cited recently (Mrak, 1969) as requiring further teratogenic evaluation. Therefore, the following toxicology review emphasizing teratology is presented for the consideration of the Committee.

Acute or General Toxicology

CAPTAN

Chicken

Diets containing 100, 1000, and 10,000 ppm captan were fed to adult white leghorn hens and roosters for a period of 90 days. The chickens receivir 100 and 1000 ppm captan showed normal food consumption, egg production, and survival when compared to the controls. Those chickens receiving the highest rate of captan showed refusal of their food and had resulting weight loss and decreased egg production. There were no significant gross

findings at autopsy in any of the test birds after 90 days of feeding on diets containing captan. Captan did not appear to alter fertility or hatchability of eggs from chickens fed diets containing 100, 1,000 or 10,000 ppm captan (Weir, 1957).

Rat

The oral LD_{50} of captan for the rat was 9,000 mg/kg body weight (Pimental, 1971).

Wildlife

The LC_{50} for mallards was $>$ 5,000 ppm; for pheasants, $>$ 5,000 ppm; for bobwhite quail, 2,000 to 4,000 ppm and for coturnix quail $>$ 5,000 ppm of captan in diets of 2-week old birds when fed treated feed for 5 days followed by untreated feed for 3 weeks (Pimental, 1971).

FOLPET

Rat

The oral LD_{50} of folpet for the rat was $>$ 10,000 mg/kg body weight (Pimental, 1971).

Fish and Wildlife

The LD_{50} of folpet for young mallards was $>$ 2,000 mg/kg body-weight when given the chemical orally in a capsule (Pimental, 1971).

The 24-hour LC_{50} for juvenile white mullet and longnosed killifish to folpet was 1.56 and 2.5 ppm, respectively (Pimental, 1971).

CAPTAFOL

Rat

The oral LD_{50} of captafol for the rat was 6,700 mg/kg body weight (Pimental, 1971). In another study, the acute oral LD_{50} of captafol

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(prepared as an 80% wettable powder) for the albino rat was found to be 2.5 ± 0.1 gm/kg body weight (Palazzola et al., 1964).

The acute dermal LD_{50} of captafol (80% wettable powder) for the albino rabbit was found to be greater than 15.4 gm/kg body weight. Also, the captafol as an 80% wettable powder was found to be moderately irritating to the ocular tissues when instilled into the eyes of the albino rabbits.

Fish

The 48-hour LC_{50} for channel catfish exposed to captafol was 31 ppm. The 24-hour LC_{50} for harlequin fish to captafol was 0.032 ppm.(Pimental, 1971)

Special Teratology Studies

CAPTAN

Chicken

Captan was injected in dimethylsulfoxide solution into either the yolk or air cell of fresh fertile white leghorn eggs in concentrations of 3 to 20 pp in the eggs. The eggs were incubated and nonviable embryos and hatched chicks were examined for gross abnormalities. In a total of 1,292 eggs, the incidence of malformations was 7.8% compared to an incidence of less than 2% in solvent-injected and uninjected control eggs. Micromelia, amelia, and phocomelia accounted for most of the deformities (Verrett, et al., 1969). The following table gives selections of the data.

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Percentage Mortality In Chicken Embryos (Air-cell Injections)

	ppm in the egg			
	18-20	10-12	6	3
Captan	93	63	45	28
Folpet	74	36	33	24
Difolatan	80	75	55	30
Tetrahydrophthalimide	38	30	7	-
Solvent Injected and Uninjected Controls		< 25%		

A test group consisting of five male and eighteen female white leghorn chickens was fed a daily dose of 75 mg technical captan/kg body weight in their diet for six weeks. An identical control group was maintained. The birds were observed for body-weight effects, food consumption, mortality, behavioral reactions and egg production with special emphasis on hatchability, viability, and abnormal physical or behavioral reactions of the chicks. Result may be summarized as follows: (1) no adverse body weight effects among birds of the test group; (2) no abnormal behavioral reactions were noted during the study for the captan-treated group; (3) no adverse effects noted on egg production and hatchability; and, (4) the one chick from the captan-treated group observed to have curled toes at hatching was normal after seven days.

That there are at best divergent opinions relative to use of chick embryos for more than preliminary screening of suspect teratogens may be illustrated by the following quote: "It is concluded that the chick embryo is of no value in the experimental investigation of thalidomide as a teratogen because the mechanism of its action in the egg appears to be entirely different to its mechanism in susceptible mammals (Carter, 1965).

Rat

Groups of five to ten pregnant female rats were given oral doses of 0, 50, 100 or 250 mg/kg body-weight/day of technical captan from days 6 through 15 of gestation or 0,500, 1,000 or 2,000 mg/kg body-weight/day from days 8 through 10. Examination of 371 foetuses obtained from the captan-treated rats revealed no significant increase in the number of abnormalities. Three and two grossly malformed foetuses were found from the rats treated with 1,000 and 2,000 mg/kg body-weight/day of captan respectively as compared with one malformed foetus in the corn oil control and none in the lower doses of captan (FAO, 1970).

Hamster

Groups, each comprising 20 pregnant female hamsters, were fed diets containing concentrations of captan sufficient to give the animals an average daily intake of 0, 125, 250 or 1,000 mg/kg body-weight of captan from days 1 through 15 of gestation. At day 15, all females were sacrificed, the young surgically removed and the foetal development and structural formation of each was examined. The incidence of abnormal effects was not greater in any test group than in the controls. However, the dose level of 1,000 mg/kg body-weight of captan resulted in a significant increase in foetal resorption (FAO, 1970).

In another hamster study, effect of single administrations of captan was compared with effect of repeated administration through organogenesis. The concentrations of test chemical were adjusted to give a uniform dose volume of 1 ml/kg body-weight. Single administration was on day 7 or day 8

of gestation. Multiple administration was from days 6 through 10, or days 6 through 8 in two instances. The total dose ranged from 200 to 2500 mg/k of body weight for captan. On day 15 of pregnancy, the animals were sacrificed uteri examined for resorption sites, and the foetuses removed, weighed, examined for external malformation, and checked for viability. Terata were developed for the captan treatments of 300, 500, 600, 750 and 1000 mg/kg body weight (Robens, 1970).

Rabbit

Four pregnant New Zealand white rabbits were given daily oral doses of 80 mg/kg body weight of captan during days 7 through 12 of gestation. Captan produced no embryotoxicity in the litters of rabbits (Fabro, et al., 1966).

New Zealand albino rabbits were given oral doses of captan in gelatin capsules of 18.75, 37.5 and 75.0 mg/kg body weight/day from gestation day 6 through gestation day 18. Ninety-five embryos from the captan-treated rabbits were examined for abnormalities. The examination of the embryos from the captan-treated does revealed no gross abnormalities, the internal structural formation was normal, and well-defined skeletal development was observed. At the level of 75.0 mg/kg, surviving young from the does treated with captan were slightly smaller than the young from untreated does. Weights of young obtained from the females treated with 18.75 and 37.5 mg/kg of captan were normal (Kennedy et al., 1967).

Thirty mature Dutch belted rabbits were divided into three groups of 10 animals each. One group received 75 mg/kg of body weight of captan daily beginning on day 6 and ending on day 16 of their gestation period.

Thalidomide was offered to one group of rabbits at 75 mg/kg of body-weight beginning on day 6 and ending on day 16 of the gestation period. The third group served as untreated controls. On day 28, each doe was sacrificed and the fetuses removed by Caesarean section. Every fetus was grossly examined for abnormalities and incubated (37°C) for six hours. Observations for viability were made at 15 minute intervals during the incubation period. Highlights of the observations were: (1) three females each in the captan and thalidomide groups showed signs of resorption while none was observed in the untreated controls; (2) study of the young did not reveal any teratogenic effects for those from the captan-dosed females and untreated control females; and, (3) fetuses from thalidomide-treated does revealed a significant teratogenic effect (Ives, et al., 1966).

Tetrahydrophthalimide was compared to thalidomide in another study similar to that conducted by Ives et al., and cited above. The pregnant rabbits receiving the subacute oral treatment of tetrahydrophthalimide had a slight increase in the occurrence of resorption sites as compared to untreated. Five of nine tetrahydrophthalmide females exhibited one to three resorption sites (total of nine) although the number of viable young was not reduced. Subsequent 24-hour survival of these young compared favorably to the untreated young. Skeletal abnormalities were found among the progeny of the thalidomide treated females (Palozzola et al., May 11, 1966)

A group of six pregnant Dutch belted rabbits was given 75 mg/kg body-weight of technical captan, orally on days 6 through 16 of gestation. Three other groups each containing five to seven New Zealand white rabbits were given 18.75, 37.5 or 75 mg/kg body-weight/day of technical captan orally on days 6 through 18 of gestation. A control group and a positive control group (75 mg/kg thalidomide) were also maintained. No malformed foetuses occurred

in any group treated with captan. An increased incidence of foetal resorption occurred in the New Zealand white rabbits given 75 mg/kg of captan. Another group of nine pregnant Dutch belted rabbits were given 75 mg/kg body-weight/day of technical tetrahydrophthalamide, a metabolite of captan, on days 6 through 16 of gestation. A slight rise in resorption sites occurred and no skeletal abnormality was observed (FAO, 1970).

Sixty female New Zealand white rabbits were divided into five groups of 12 animals each. After artificial insemination, the animals were assigned to the groups including untreated control, 20, 40 and 80 mg/kg body-weight/day of captan and the fifth group receiving 100 mg/kg body-weight/d of thalidomide. These treatments were administered by gelatin capsule daily from day 6 to day 18 of gestation. On day 30 of the gestation period, all females were sacrificed and the fetuses delivered by Caesarean section. Ovaries and uteri of each female were examined for corpora lutea, implantation sites, resorptions and gross pathology. The numbers of viable and nonviable fetuses were recorded and surviving young were incubated for observation 24 hours. All fetuses were examined for external abnormalities; and, later subjected to detailed necropsy, evidence of visceral anomalies, and examined for skeletal abnormalities. The data suggested a slight increase in resorption in all treated groups except the 40 mg/kg of captan. Visceral examinations revealed a slight increase in teratological changes in young from those treated with thalidomide (Benson, 1967).

Groups of nine pregnant New Zealand white rabbits were given captan at dose levels of 37.5, 75 or 150/mg/kg body-weight from days 6 through 16 of gestation. Thalidomide served as a positive control at levels of 75 and 150 mg/kg body-weight and produced the expected teratological response.

Captan at 75 mg/kg caused nine malformed young from 75 implantations of nine pregnant does. At the dose level of 37.5 mg/kg., captan produced one malformed foetus from 49 implantation sites (McLaughlin et al., 1969).

Monkey

Groups, each consisting of seven pregnant Rhesus monkeys, were given daily oral doses of 6.25, 12.5 and 25.0 mg/kg body-weight of captan on days 22 through 32 of gestation. Thalidomide was used as the positive control at dosage levels of 5 mg/kg body-weight/day in six animals and at 10 mg/kg body-weight/day in four animals. Foetuses not aborted were delivered by Caesarean section on approximately the 84th day of gestation and examined for organ and skeletal defects. There was foetal mortality in three of the seven monkeys on the 25 mg/kg treatment of captan. The foetal mortality of the parent colony not fed captan was 13.2 percent for 439 conceptions. There was no abnormality of any foetus in either of the three captan treatments (Courtney, 1968).

In another study the teratological potential of captan in Rhesus monkey (Macaca mulatta) and the stumptailed macaque (Macaca arctoides was investigated. A total of seven pregnant monkeys were dosed at the levels of 10,25 and 75 mg/kg body-weight daily on days 21 through 34 of gestation. One abortion occurred at the 75 mg/kg level but there were no malformations. Thalidomide was used as a positive control to evaluate the suitability of the animals for teratological study. Skeletal deformities occurred among five of the seven Rhesus foetuses and among all five of the stumptailed macaque foetuses which were recovered from those on thalidomide dosages. Also, four abortions occurred for the thalidomide dosed stumptailed macaque and all were attributed to thalidomide (Vondruska, 1969).

FOLPET

. Chicken

Folpet was injected in dimethylsulfoxide into the yolk or egg cell of fresh fertile chicken eggs at levels which varied from 3 to 20 mg/kg egg-weight. The eggs were incubated and nonviable embryos and hatched chicks were examined for gross abnormalities. Of a total of 830 eggs injected with folpet the incidence of malformation was 8.19 percent. The metabolites of folpet, phthalimide (305 eggs) and phthalic acid (290 eggs) were also injected under similar conditions using dimethylsulfoxide as a solvent for phthalimide and ethanol for phthalic acid. A control group of over 1500 eggs was injected with dimethylsulfoxide alone and another control group of several thousand eggs with ethanol alone. The malformations were 3.93 percent for phthalimide, 3.10 for phthalic acid, and less than 2.0 percent for the controls. Most of the deformities were micromelia, amelia, and phocomelia (Varrett et al., 1969).

Rat

Pregnant Charles River strain female rats were given 0, 100 (10 animals) or 500 (5 animals) mg/kg body-weight of technical folpet by oral intubation on gestation days 6 to 15 for the lower dose and gestation days 8 to 10 for the higher dose. Trypan blue was used as a positive control given as subcutaneous injection at 50 mg/kg body-weight on days 8 to 10 of gestation. All rats were sacrificed on the 20th day of gestation. A total of 169 foetuses were examined and revealed no significant increase in incidence of abnormalities in the groups receiving folpet. The foetuses from folpet-dosed rats had normal internal structures, the young were present in normal numbers and were well formed. The trypan blue-dosed females produced malforme young (FAO, 1970).

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A group of 10 pregnant female rats (Charles River and Sprague Dawley derived strain) received oral doses of 100 mg/kg body-weight/day of folpet from day 6 to 15 of gestation. Another group of four pregnant female rats was given oral doses of 500 mg/kg body-weight/day from day 8 to day 10 of gestation. There was no evidence of any abnormalities related to the administration of folpet based upon examination of the following foetuses: 120 foetuses from the 100 mg group; 49 foetuses in the 500 mg/kg group; and, 200 foetuses from the untreated control (FAO, 1970).

Hamster

Golden Syrian hamsters were used to compare the effects of single administration of folpet with effects of repeated administration to pregnant females through organogenesis. Single administration was indicated to be a more sensitive method of detecting teratogenicity. The concentrations were adjusted to give a uniform dose level of 1 ml/gm body-weight. The single administration was made on day 7 or day 8 of gestation; and, the multiple administration was from days 6 through 10 of gestation, or days 6 through 8 in two instances. The females were sacrificed on day 15 of pregnancy and uteri examined for presence of resorption sites. The foetuses were removed, weighed, examined for external malformations, checked for viability, and those foetuses showing gross abnormalities were further examined for bone defects. Folpet doses producing numbers of terata were the 500, 600, 700, 800, 900, and 1,000 mg/kg body-weight. By comparison the controls receiving no chemical had 0.4 percent terata (Robens, 1970).

Groups of 10 pregnant Syrian golden hamsters were fed technical folpet at dietary levels approximately equivalent to 0, 125, 250, 500 or 1,000 (eight animals) mg/kg body-weight per day from gestation days 4 to 15 inclusiv

On day 15 of gestation, all animals were sacrificed and foetal examinations made. Maternal body-weight gains were decreased over the feeding period in the 250 and 500 mg/kg groups while at the 1,000 mg/kg level there was a weight loss recorded. There was an increase in the number of resorption sites at the two highest dose levels compared with the control group. Growth appeared to be retarded for the foetuses from all test groups. The mean number of foetuses per litter was reduced at the two highest dose levels. There were no gross or skeletal abnormalities attributable to folpet at any of the levels used (FAO, 1970).

In a companion study to that summarized above, folpet was given to the hamsters by intubation. The hamsters were given a single dose of 0 (11 pregnan females), 125 (9 pregnant females), 250 (5 pregnant females), and 500 (8 pregna females) mg/kg body-weight. Half of each group was intubed on day 7 and the remainder on day 8 of gestation. A positive control group received 1000 mg thalidomide/kg body-weight on day 7 of gestation. The number of foetal resorption sites was higher than normal for all groups of this experiment. The highest resorption incidence was in the 125 mg/kg group (5.8 per litter) and the low incidence was in the 500 mg/kg group (2.5 per liter). The number of young per litter was lower in all test groups than in the control. No gross physical or skeletal anomalies were found in the test groups which could be associated with folpet. Further, no abnormalities were found in the thalidomide-treated group (FAO, 1970).

Rabbit

Folpet was given to groups of pregnant New Zealand albino rabbits at dose levels of 0, 18.75 (5 animals), 37.5 (5 animals), and 75 (7 animals)

mg/kg body-weight on gestation days 6 to 18 inclusive. The treatments were administered by gelatin capsule. Positive control animals were given thalidomide at various dose levels. On gestation day 29 each doe was sacrificed and the young removed by Caesarian section. Folpet produced signs of toxicity in the female rabbit. Females treated with folpet at the two higher dose levels did not gain as much weight as would be expected during gestation; and, the incidences of foetal resorption at these same higher levels was greater than that observed for the untreated animals. There appeared to be a compound-related effect on mortality. Examination of 80 embryos from the folpet-treated females revealed no gross abnormalities, the internal structural formation was normal, and well-defined skeletal development was observed. Embryos from the positive control females on thalidomide produced malformed young (Kennedy et al., 1967).

Groups of pregnant New Zealand white rabbits were given folpet at dose levels of 75 and 150 mg/kg body-weight. Thalidomide was given to a positive control group at the same dose levels. Thalidomide produced a teratological response whereas folpet did not (McLaughlin et al., 1969).

A teratogenic study with Dutch belted pregnant female rabbits was established to compare folpet, thalidomide and an untreated control group. Each group consisted of 10 animals. All does of the folpet and thalidomide groups received oral doses of 75 mg/kg body-weight/day beginning on day 6 and extending through day 16 of the gestation period. Dosing was by means of gelatin capsules. On day 28 of gestation, each female was sacrificed and the foetuses removed by Caesarian section. Every foetus was examined for gross abnormalities and observed for viability. The study did not reveal any teratogenic effects due to folpet treatment whereas the thalidomide did cause a teratogenic effect (Ives et al., 1966).

Thirty pregnant Dutch belted rabbits were divided into three groups of 10 each to determine teratogenicity of phthalimide. Comparison was made with thalidomide and untreated control groups. The thalidomide and phthalimide groups (10 animals each) were given 75 mg/kg body-weight via gelatin capsule from day 6 through day 16 of gestation inclusive. On day 28 of gestation each doe was sacrificed and young removed by Caesarian section. Immediately the foetuses were examined for abnormalities, observed for viability for 24 hours, and skeletal tissue examined. Other observations were to record total implantation sites, number of resorptions and number of normal and abnormal young. The study indicated phthalimide at rate administered had no teratogenic effect on the young nor any deleterious effect upon the parental females. Skeletal abnormalities were noted among the young of the thalidomide-treated group (Palazzola et al., May 11, 1966).

Monkey

The teratogenic potential of folpet was evaluated with the Rhesus monkey (Macaca mulatta) and the stumptailed macaque (Macaca speciosa). Thalidomide was used as a positive control for the study. At least four pregnant monkeys of each species were dosed with folpet at each level of 10, 25 and 75 mg/kg body-weight from gestation day 21 to 34. The foetuses were recovered by Caesarian section during the 12th week of gestation. All foetuses of the folpet doses were grossly normal except one abnormal Rhesus foetus from both the 25 and 75 mg/kg doses, each of which had 13 pairs of ribs. The extra pair of ribs, though not normal, was considered a chance occurrence. Thalidomide as a positive control was given as follows: (1) 5 mg thalidomide /kg body-weight to three stumptailed macaque females during gestation days 26-28 and 24-30; (2) 10 mg thalidomide /kg body-weight to six stumptailed macaque during gestation days 25-27, 24-30 and 23-29; and, (3) 10 mg

thalidomide /kg body-weight to 11 Rhesus monkeys during gestation days 25-27. Skeletal deformities occurred among six of the eight Rhesus foetuses and all five of the stumptailed foetuses from females on the thalidomide treatments. Also, four abortions occurred for the stumptailed macaque and three for the Rhesus monkeys on the thalidomide doses. No other abnormal reactions were seen which could be attributed to thalidomide or folpet (Vondruska, December 1, 1969).

CAPTAFOL

Chicken

Captafol was injected in dimethylsulfoxide solution into either the yolk or air cell of fresh fertile eggs at levels from 3 to 20 mg/kg egg weight. The eggs were incubated and nonviable embryos and hatched chicks were examined for gross abnormalities. In a total of 270 eggs treated with captafol, the incidence of malformations was 6.67 percent compared to the control value of 1.6 percent for 1500 eggs injected with dimethylsulfoxide alone. In the same experiment the metabolite tetrahydrophthalimide was also injected and the incidence of malformation was 4.78 percent. The epoxy derivative of captafol was also tested for its effect. Of 115 eggs into which was injected the captafol epoxide, the incidence of malformation was 15.05 percent. In all cases the malformations consisted mainly of micromelia, amelia and phocomelia (Verrett et al., 1969).

Rat

Groups of 8 male and 16 female rats were fed captafol at 0, 50 (raised to 100 after first generation), 250 (raised to 500 after first generation),

and 1000 ppm in the diet in a three-generation reproduction study. There were no adverse effects on body-weight gain, mortality, or organ weights of parental animals or reproductive performance, fertility and lactation indices, litter-size, or number of stillbirths in any test group. Pup survival in the test groups at various intervals in the lactation period was not significantly different from the control group. Weanling body-weights in the 1000 ppm group were depressed in both males and females in the first and third generations. Weanlings of the second generation showed only slight weight depression. Gross examinations and histopathology carried out on parental animals and F_3b weanlings in the 0 and 1000 ppm groups revealed no changes that could be attributed to captafol (Kennedy et al., January 24, 1966).

A group of nine pregnant female rats was given doses of 100 mg/kg body-weight/day of captafol orally from day 6 to day 15 of gestation and another group of five pregnant rats was given 500 mg/kg body-weight from day 8 to day 10. Examination of 180 foetuses revealed no gross malformations (FAO, 1970).

Hamster

Pregnant female golden Syrian hamsters were used to evaluate the teratogenic and embryotopic effects of captafol when given as a single oral administration compared with repeated administrations through organogenesis. Single administration was indicated to be a more sensitive method of detecting teratogenicity. The concentrations were adjusted to give a uniform dose level of 1 ml/gm body-weight. The single administration was made on day 7 or day 8 of gestation; and, the multiple administration was from days 6 through 10 of gestation, or days 6 through 8 in two instances. The females were sacrificed on day 15 of pregnancy and uteri examined for

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presence of resorption sites. The foetuses were removed, weighed, examined for external malformations, checked for viability, and those foetuses showing gross abnormalities were further examined for bone defects. Captafol single doses producing terata were the 200, 300, 400, and 500 mg/kg body-weight. Captafol repeated administrations producing terata at the 500 and 1000 mg/kg body-weight doses. By comparison the controls receiving no chemical had 0.4 percent terata (Robens, 1970).

Rabbit

Groups of 10 pregnant Dutch belted rabbits received daily oral doses of 0 or 75 mg/kg body-weight of technical captafol. A third group was given thalidomide at 75 mg/kg body-weight. Dosing, administered by gelatin capsule, began on day 6 and ended on day 16 of the gestation period (the day of conception being day 0). On day 28, each doe was sacrificed and the foetuses removed by Caesarian section. The rabbits given captafol lost weight over the period of treatment. One doe in this group aborted eight young and another showed one resorption site. Three does in the thalidomide group showed evidence of resorption. Of the viable young, 86 percent from the group given captafol survived a six-hour incubation (37°C) period compared with 100 percent in the control group. No abnormalities were seen among 74 foetuses in the group given captafol. Foetuses from the group given thalidomide showed significant teratogenic effects (Ives et al., 1965).

In another study, groups of 10 pregnant New Zealand albino rabbits were given technical captafol at doses of 37.5, 75.0, 112.5 or 150 mg/kg body-weight of thalidomide. All doses were administered via gelatin capsule. On day 29 each doe was sacrificed and the young were removed by Caesarian section, weighed and observed for abnormalities. At the lowest level of captafol tested, there was no maternal mortality and the animals gained

weight, although not as much as the control. Resorption sites occurred in two of the ten females (three sites) on low-level captafol. Examination of 62 foetuses from this same group revealed no abnormalities. At all the higher dose levels of captafol, toxic effects were seen in the mothers. Deaths occurred in each group and resorption sites were prevalent in the survivors. However, all young delivered in all three high level captafol groups were free of gross teratological effects and survived the 24-hour incubation period. In the group given thalidomide, 32 of 55 foetuses showed abnormalities (Jackson et al., 1967).

Monkey

Captafol was evaluated as a teratogenic agent with adult female Rhesus monkeys (Macaca mulatta). All treatments were by oral intubation. Details of the experimental plan for captafol treatments were: (1) 6.25 mg/kg body-weight/day to seven monkeys on gestation days 22-32; (3) 12.5 mg/kg body-weight day to one monkey each on gestation days 66-80, 81-95, and 86-100; and, (4) 25 mg/kg body-weight/day to seven monkeys on gestation days 22-32. Thalidomide was used as a positive control at 10 mg/kg body-weight day and was given on days 25, 26 and 27 of gestation to seven pregnant monkeys. Careful examination of 19 foetuses via gross observation, x-ray and skeletal examination followed alizarin red S staining revealed no abnormalities grossly. Internal structural formation, observed both grossly and by evaluation of organ weight and organ to body-weight ratio data, was normal. Well-defined skeletal development was observed upon examination of fetal x-rays and following cleaning and staining procedures. Fetal mortality (resorption or abortion) was observed among 2 of 7 females treated at the 25 mg/kg level of captafol. No mortality was observed for captafol at the 6.25 and 12.5 mg/kg levels. Five of seven fetuses recovered from females on the thalidomide treatment exhibited limb abnormalities (Kennedy et al., 1968).

Summary and Evaluation--Teratology

The teratology papers reviewed are summarized by animal in the following table. Note the comparison of numbers of studies versus those reporting significant teratological response.

Chemical	Animal	Number of Studies Reported	Number of Studies Reporting Significan Teratology
Captan	Chicken Embryo	1	1
	Chicken	1	0
	Rat	1	0
	Hamster	2	1
	Rabbit	6	1
	Monkey	2	0
Folpet	Chicken Embryo	1	1
	Rat	2	0
	Hamster	3	1
	Rabbit	3	0
	Monkey	2	0
Captafol	Chicken Embryo	1	1
	Rat	2	0
	Hamster	1	1
	Rabbit	2	0
	Monkey	1	0
Tetrahydrophthalimide			
	Chicken Embryo	1	1
	Rabbit	1	0
Phthalimide	Rabbit	1	0

Examination of the above table of studies indicates the chicken embryo technique responds with a teratological determination more consistently than tests with laboratory animals. The rat, chicken and two species of monkey were the only animals not to give at least one significant malformation response in a total of thirty-four reports tabulated for this review.

In conclusion, the current estimate of temporary acceptable daily intake for man (FAO, 1970) is compared with the highest level causing no toxicological effect and levels causing effects to monkey for captan, folpet and captafol. See attached Table 1 for the comparisons.

TABLE 1

Comparison of Temporary Acceptable Daily Intake for Man
With Levels of No Effect and Effect Evaluated in Monkeys

Pesticide	Estimated Temporary Accepted Daily Intake for Man *	Level Causing No Toxicological Effect*	Level Causing Resorption or Fetal Mortality*	Level Causing Abortions*	Level Causing Malformations*
Captan	0.125	12.5	25.0	75.0	None
Folpet	0.16	10.0	None	None	25.0 and 75.0-- one animal at each level had a 13th pair of ribs
Captafol	0.05	12.5	25.0	25.0	None

Mg/kg body-weight/day.

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