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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: October 14, 1981

003728

SUBJECT: Toxicology Review of Benomyl

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Attached please find an updated review of the toxicology profile on Benomyl. The review contains seven sections which have been revised to accommodate changes in the teratogenic NOEL and the oncogenic risk from dietary exposure. The revised dietary exposure risk data was sent to you with the memo of October 1. The seven sections in this package are:

1. Preliminary review of oncogenicity
2. Cancer risk calculations
3. Application of calculations
4. Teratogenic, spermatogenic and oncogenic risks to applicators
5. Field Re-entry or post-application exposure
6. Teratogenic and reproductive effect
7. Neurotoxicity review

Attachment

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6. Benomyl Teratogenic and Reproductive Effects

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Introduction

In its rebuttable presumption against registration of benomyl set forth in PD 1, the Agency cited studies in which teratogenic effects were obtained by administration of benomyl to laboratory animals by gavage. In PD 2/3, the arguments presented in rebuttal of the Agency position were successfully rejected. The Agency chose to use the unrebutted no observable effect level of 7.5 mg/kg obtained from an inhalation study (see Table I, study No. 10).

The Agency has since received more data and now has reason to revise the no observed effect level (NOEL) to 30.0 mg/kg, (see Table I, study No. 17). All of the studies received to date concerning teratogenicity and reproductive effects are placed in perspective by their listing in Table I.

a. Route of Administration in Animals

Table II compares the results obtained for teratogenicity when benomyl or its active metabolite MBC are administered by gavage or through dietary treatment using similar strains of rats. It is seen in Table II that the gavage method is more effective than dietary administration at inducing terata in Wistar rats as well as in CHR-CD rats. When MBC was administered by diet and the results compared with those from benomyl administration, MBC gavage was more effective at producing terata.

The results of dietary administration of benomyl in rats were found to be at variance with those obtained by gavage administration. This variance was observed when the result of three different laboratories were compared (Kavlock, 1979) and did not appear to be related to the rat species employed. The question of gavage or intubation versus dietary administration was addressed in PD 2/3 and the rebuttal argument against the gavage method was rejected by the Agency on the grounds that gavage is an appropriate method of administration and is probably the most common method used in teratology testing (Burnam, 1978). The use of gavage eliminates problems of palatability, drug stability, nutrient integrity and consumption calculation associated with dietary administration (EPA, 1980). Furthermore, gavage assures relevance of treatment to the human condition, since rodents, by preference, eat very frequently, even continuously, during waking hours, whereas humans dine at relatively orderly intervals during the day. Therefore, the "peaking" of blood levels of treatment chemicals in rodent species which results from intubation more clearly parallels the human situation than continuous uptake of chemical in a dietary admixture.

Two Dupont studies were done using pregnant CHR-CD® rats to determine the concentrations of the parent compound, benomyl, its metabolite MBC, 4-OH MBC and 5-OH MBC in maternal blood and fetal tissue. One study involved administration by gavage and the other used dietary administration (admixture in the diet). Peak benomyl/MBC concentrations in embryos in the gavage group was well above 2 ppm on day 12 of gestation. Dietary benomyl/MBC concentrations in embryos were below the limits of detection (< 0.3 ppm) suggesting that the lack of teratogenic effects in embryos from a dietary regimen of benomyl administration was due to lack of embryo contact with benomyl.

TABLE I (cont.)

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TERATOGENIC AND REPRODUCTIVE EFFECTS OF BENOMYL

Study Number	Species	Treatment	NOEL/LEL	Terata Observed	Reference
14.	Wistar Rat	0-125 mg/kg/day on days 7-16 of gestation-Gavage	LEL = 62.5 mg/ NOEL = 31.2 mg/kg/day	Microphthalmia** and Fetal mortalities bet. low-high dose. Significant embryonic resorption at highest doses. Fetal weights significantly reduced above 31.2 mg/kg/day.	Kavlock et al 1980
15.	Wistar Rats	Dietary 0-500 mg/ kg/day days 7-16 gestation	LEL = 298 mg/ kg/day (calculated) NOEL = 169 mg/kg/day (calculated)	Maternal wt. change treatment related at highest doses. No dose-related incidences of anomalies or malformations	Kavlock et al 1980
16.	Wistar Rats	Post-natal teratology study - Gavage administration to lactating dams - gestation day 7 - lactation day 15	LEL = 62.5 mg/ kg/day NOEL = 31.2 mg/kg/day	Reduction in wt. of testes, ventral prostate, & seminal vescicles in pups	Kavlock et al 1980
17.	CHR-CD Rats	Gavage 0-125 mg/kg /day	LEL = 62.5 mg/ kg/day NOEL = 30 mg/ kg/day	Unilateral microphthalmia at 10 mg/kg/day. Embryotoxicity at 62.5 mg/ kg/day above	Staples 1980
18.	CHR-CD Rats	Dietary MBC days 6-15 gestation; 0-10,000 ppm	NOEL = 5000 ppm LEL = 7,500 ppm (in mg/kg/day, = 250 and 375 respectively	Not embryotoxic or teratogenic. Slightly lower, not statistically significant fetal wts at 7,500 ppm	Haskell Lab report No 466-70 1978
19.	Sprague-Dawley Rats	Gavage-days 8-15 of gestation-dose MBC = 9.55 mg/kg; dose benomyl = 116 mg/kg	NOEL and LEL not calculated	Terata produced - exencephaly (MBC-treated) and other malformations	Delatour & Richard 1976

* MBC fed in diet

** Single litters with microphthalmia in 15.6 , 62.5 and 125 mg/kg/day groups.

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TABLE I

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TERATOGENIC REPRODUCTIVE AND RELATED EFFECTS OF BENOMYL OR MBC

Study Number	Species	Treatment	NOEL/LEL	Terata Observed	Reference
1.	Wistar Rats	1) 0, 62.5, 125, 250, 500 mg/kg/day during days 7-15 gestation 2) as above, days 1-20 gestation Gavage	NOEL = 62.5 mg/kg/day LEL = 125 mg/kg/day	Brain hernias, hydrocephalia, microphthalmia, anophthalmia	Schtenberg & Torchinski 1972
2.	Wistar Rats	145 mg/kg, day 12 gestation Gavage	NOEL = None LEL = None Calculated insufficient data	Teratogenic	Torchinski 1973
3.	Charles River, CD Rats	5 mg/kg - 400 mg/kg/day Dietary through gestation day 15	NOEL = 400 mg/kg/day (H.D.T.) LEL = > 400 mg/kg/day	Not teratogenic Definitive conclusion not drawn because ingested dose not accurately measured	Sherman, et al 1975
4.	Rats	> 3400 mg/kg Gavage (acute and subacute tests)	NOEL = < 3400 mg/kg/day LEL = 3400 mg/kg/day (L.D.T.)	Degeneration of germinal tissue & aspermatogenesis Testes = 1° target of Benomyl (mature rats)	Shermal & Kraus, 1966
5.	Rats	670 mg/kg (single dose) Gavage (acute test)	See study #8	Reduction of sperm (mature rats)	Sherman & Kraus, 1966
6.	Rats	10 doses, 200 mg/kg/dose Gavage (subacute test)	See study #8	Reduction of sperm (mature rats)	Sherman & Kraus, 1966
7.	Dogs	0, 100, 500, 1500 and 2500 ppm Dietary chronic 2 yr. feeding *	NOEL = > 2500 ppm LEL = > 2500 ppm	No effect on sperm production (mature animals)	Sherman, et al 1969,1970

* MBC fed in diet

TABLE I (cont.)

TERATOGENIC AND REPRODUCTIVE EFFECTS OF BENOMYL

Study Number	Species	Treatment	NOEL/LEL	Terata Observed	Reference
8.	Rats	0, 100, 500 ppm Dietary chronic feeding	NOEL = > 2500 LEL = > 2500	No effect on sperm production (mature animals)	Sherman, et al 1969, 1970
9.	Rats - 3 generation reproductive studies	Up to 2500 ppm in diet *	NOEL = 500 ppm LEL = 2500 ppm	No effect on fertility index - no pathol. changes attributable to MBC in diets - weights sl. decreased at 2500 - 10,000 ppm in fetuses	Sherman et al 1975
10.	Rats	Inhalation 33 mg/kg	LEL = 33 mg/kg/day NOEL = 7.5 mg/kg/day	Reduction of spermatogenic activity (mature dogs)	Hornberger 1969
11.	Dogs	Inhalation 82 mg/kg	LEL = 82 mg/kg/day NOEL = 32 mg/kg/day	Reduction of spermatogenic activity (mature dogs)	Littlefield 1969
12.	Wistar Rats	0-500 mg/kg/day; days 6-15 gestation Gavage	LEL = 62.5 mg/kg/day NOEL = < 62.5 mg/kg/day (L.D.T.)	Dose-related fetal wt decrease + increase in malformations -CNS herniations & reduction defects of extremities, lack of eye bulges	Short et al 1979
13.	CD-1 Mice	200 or 400 mg/kg/day in corn oil, days 8-12 of gestation Gavage	LEL = 200 mg/kg/day NOEL = < 200 mg/kg/day	Complete resorption of 63% at 400 mg/kg/day: litter size 59% of controls. At 200 mg/kg/day wts of pups diminished by 11% herniations of CNS & reduction of extremities	Kavlock et al 1979

* MBC fed in diet

TABLE II

COMPARISON OF TERATOLOGY EFFECTS OF DIETARY OR GAVAGE ADMINISTRATION OF BENOMYL IN SIMILAR RAT STRAINS

Rat Strain	Study Number	Gavage (mg/kg/day)	Dietary (mg/kg/day)	Study Number
Wistar Rats	1	NOEL = 62.5 LEL = 125	NOEL = 169.0 LEL = 298.0	15
	12	NOEL = < 62.5 LEL = 62.5		
	14	NOEL = 31.2 LEL = 62.5		
CHR-CD Rats	17	NOEL = 30.0 LEL = 62.5	NOEL = 400 LEL = >400	3
			* NOEL = 250 LEL = 375	18

* MBC administered

b.) Reproductive Effects

Table I lists studies demonstrating effects on testicular tissue as well as teratogenicity studies. Studies 4-8, 10 and 11 were discussed in PD 1 and PD 2/3; their validity was not questioned, (effects in mature animals). Study No. 16, a postnatal study, clearly showed similar effects in rat pups. The pups showed permanent reduction in the weight of testes, ventral prostate and seminal vesicles. The manner in which the experiment was conducted is as follows: Groups of pregnant animals from each dosage group of a gavage teratogenicity test (Wistar Rats) were reserved for further testing. After birth, the lactating mothers were continuously gavaged throughout the lactation period. At maturity, the grown pups were necropsied, and at that time the testicular effects were noted. From the details of that experiment, it is not known whether the testicular effect might be seen in a mature rat if gavage of the mother were not done during lactation, or if gavage administration of benomyl had been done only during the lactation period and not during gestation as well. It is interesting to note that spermatogenic effects were observed in mature animals as a result of inhalation exposure (Table I, Study No. 10). It is on the results of the latter test that the 7.5 mg/kg/day NOEL for spermatogenic effects is based. Similar spermatogenic effects were seen in other studies (Table I, studies 4, 5, 6 and 11).

c.) Teratogenic Effects

At high doses of benomyl, malformations in brain (central nervous system herniations, Table I studies 1, 12 and 13). These effects were seen with MBC administration as well (Table I, study 19).

Another key teratogenic effect was anophthalmia or microphthalmia, the latter manifested bilaterally or unilaterally. The historical control incidence of this effect was found to be 1 in 1,000 (Staples, 1980, Haskell Lab. report 649-80). The eye effects were seen in three studies (Table I, studies 1, 14 and 17) and suggested from the data reported by Short et.al., 1979 (Table I, Study 12) in their report describing "absence of eye bulges". In fact, two studies reveal the eye effects to show a dose-response relationship with the cut off for statistically significant values in both studies at 62.5 mg/kg/day (Table I, Studies 16 and 17). Both studies showed occasional microphthalmia at levels below 62.5 mg/kg/day but not at statistically significant values.

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d.) Teratogenicity Safety Factors for Dietary Exposure for Benomyl.

The following (Table III) demonstrates the calculation of safety factors for Benomyl through dietary ingestion based on single serving sized portions of commodities treated at tolerance levels with that chemical. The NOEL (no observed effect level) of 30 mg/kg is based on the figure shown in Table I, study 17. The data show that apricots, cherries, nectarines, oranges, peaches, pineapple and raisins have a safety factor of 1000 or less. Apples, blueberries, grapes, grapefruit, mushrooms, pears, plums and tomatoes have a safety factor of only 2000 or less. Depending upon the percentage of a particular commodity crop treated, it is not impossible for an individual to exceed the maximal permissible yearly intake, based on the safety factors cited above. For a pregnant woman at a stage of early gestation, this could be a severe embryonic health hazard.

Table IV shows similar safety factor calculations for Thiophanate-Methyl, which has a metabolite in common with that of Benomyl, namely, MBC. Because the number of tolerances issued is smaller for Thiophanate-Methyl than for Benomyl, the list of commodities is concomitantly shorter. Tolerances are the same for the stone fruits for both chemicals, so that the resultant safety factors are also similar and present a similar potential human hazard.

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TABLE III

Benomyl
Single Serving Dietary Exposure

Food Commodity	Serving Size (kg)	Tolerance[a] (mg/kg)	Benomyl (mg/serving)	Benomyl (mg/kg BW[b])	Safety Fact (30.0 mg/kg/da
Apples	0.212	7.00	1.48	0.025	1,200
Apricots	0.114	15.00	1.71	0.029	1,035
Avocados	0.375	1.00	0.33	0.0063	4,762
Bananas	0.136	0.20	0.027	0.0005	60,000
Beans	0.072	2.00	0.14	0.0024	12,500
Blueberries	0.145	7.00	1.02	0.017	1,765
Celery	0.160	3.00	0.48	0.0083	3,615
Cherries	0.145	15.00	2.18	0.036	833
Cucumber	0.144	1.00	0.144	0.0024	30,000
Eggs	0.057	0.10	0.0057	0.0001	30,000
Grapes	0.081	10.00	0.81	0.014	2,143
Grapefruit	0.121	10.00	1.121	0.020	1,500
Mangoes	0.165	3.00	0.50	0.008	3,750
Meat, Beef Fatty	0.113	0.10	0.011	0.0002	150,000
Melons, Cantalopes	0.140	1.00	0.16	0.0027	11,111
Melons, Watermelon	0.160	1.00	2.45	0.0027	11,111
Milk, Cow	0.244	0.10	2.63	0.0004	75,000
Mushrooms	0.095	10.00	0.03	0.016	1,875
Nectarines	0.150	15.00	1.26	0.038	790
Nuts, Cashew	0.140	0.20	5.48	0.0005	60,000
Oranges	0.245	10.00	2.45	0.041	732
Peaches	0.174	15.00	2.63	0.044	682
Peanuts	0.152	0.20	0.03	0.0005	60,000
Pears	0.180	7.00	1.26	0.021	1,429
Pineapple	0.155	35.00	5.43	0.090	333
Plums	0.070	15.00	1.04	0.018	1,667
Poultry, Chicken	0.140	0.10	0.014	0.0002	150,000
Pumpkins	0.140	1.00	0.14	0.0023	13,043
Raisins	0.142	50.00	7.10	0.118	254
Rice	0.100	5.00	0.50	0.0083	3,615
Soybean Oil	0.014	0.20	0.0028	0.00005	600,000
Squash	0.222	1.00	0.222	0.0037	8,108
Strawberries	0.075	5.00	0.36	0.0063	4,762
Tomatoes	0.181	5.00	0.91	0.015	2,000

[a] 40 CFR 180.294
[b] 60 kg Woman

BENOMYL

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7. Review of Neurotoxicity Studies with Benomyl and MBC

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No indications that Benomyl or MBC were involved in neurotoxic effects from information received at the time of the Agency's preparation of PD 1 or PD 2/3. Since that time, Dupont has submitted three studies to determine the potential neurotoxicity of Benomyl and its metabolite MBC. Two of the studies were concerned with effects of Benomyl administration on hens and one was concerned with MBC administration in hens. The studies are presently under Agency review, but will be briefly summarized here.

In the first study with Benomyl, five groups of 10 White Leghorn hens were administered by gavage single doses of the following test materials in 20 ml corn oil/kg respectively: o mg/kg (vehicle control), 750 mg/kg tri-o-tolyl phosphate (TOTP, positive control), and 500 mg/kg, 2500 mg/kg and 5000 mg/kg benomyl (experimentals). Animals were observed for pharmacotoxic symptoms including neurotoxicity. Surviving animals were sacrificed, autopsied and organs examined grossly and selected nerve tissue from spinal cord and peripheral (sciatic) nerves examined histologically for microscopic neurotoxic effects. Weights of all birds were monitored during the study.

None of the vehicle controls showed any symptoms. High dose benomyl-treated hens had one death, decreased activity and diarrhea, and some neurotoxic symptoms (altered behavior). The high dose and mid dose benomyl-treated hens (5000 mg/kg and 2500 mg/kg, respectively) showed some compound related effects on microscopic examination of spinal cord and peripheral nerves. Positive controls (TOTP treatment) displayed the appropriate spectrum of nerve tissue degeneration known to be produced by that chemical. However, at the conclusion of the experiment, the study was declared inconclusive, due to evidence of underlying disease in the hens. The disease state was determined by a group of pathologists who examined the histological slide preparations of nerve tissues and identified pathological characteristics of Marek's disease.

A second benomyl study was then initiated, employing only hens which had been vaccinated against Marek's disease, New Castle disease, Avian Encephalomyelitis and Brochitis. The protocol employed for the second benomyl study was the same as that described above, except that the dosage for the TOTP positive controls was increased from 750 mg/kg to 1200 mg/kg.

Five of the 10 high dose benomyl treated (5000 mg/kg) hens died between 6-9 days following treatment. The deaths were considered to be the consequence of acute toxicity of benomyl. Acute neurotoxicity symptoms were seen in the high dose benomyl-treated survivors, and in TOTP-treated hens. Symptoms in high dose benomyl-treated survivors were primarily of decreased activity. TOTP treated hens showed symptoms of delayed neurotoxicity, which benomyl treated hens did not. The neurotoxic behavior symptoms displayed early in the 5000 mg/kg benomyl treated hens was

attributed to acute toxic effect of the chemical. Hens treated with mid and low doses of benomyl (2500 mg/kg and 500 mg/kg, respectively) appeared normal and behavior was normal. No treatment related gross pathological effects were seen in any hen as sacrifice and autopsy in benomyl treated hens. Microscopic examination of spinal cord and sciatic nerves showed a spectrum of (expected) positive findings characteristic of TOTP treatment in the TOTP treated hens. Some degenerative changes were seen in negative control nerve tissue as well as in some 500 mg/kg treated and 2500 mg/kg treated benomyl hens - and none were seen in similar tissues from 5000 mg/kg benomyl treated hens.

In the MBC study, three groups of 10 White Leghorn hens were administered by gavage single doses of MBCC in 20 mg/kg corn oil (vehicle) as follows: 0 mg/kg (vehicle control), 750 mg/kg Tri-o-tolyl phosphate (TOTP, positive control) and 5000 mg/kg MBC (experimental). Another MBC study was initiated three weeks later, employing four groups of 10 hens as follows: 0 mg/kg (vehicle control), 750 mg/kg TOTP (positive control), 500 mg/kg MBC and 2500 mg/kg MBC.

Two high dose hens died after 10 and 11 days respectively, both showing signs of salivation prior to death. One low dose hen was sacrificed moribund due to an accident. Salivation appeared in TOTP treated hens 2-3 days after treatment (4/10 hens). Neurotoxicity symptoms appeared in TOTP treated hens on days 7-14 and persisted in 8/10 hens until the study was terminated. Hens treated with 500 and 2500 mg/kg MBC showed no such symptoms. At autopsy, treatment related effects were seen in several hens from the TOTP group and the 5000 mg/kg benomyl treated birds. No treatment related gross organ lesions were seen in 500 mg/gk or 2000 mg/kg MBC treated hens. No compound related changes were seen on microscopic examinationof spinal cord or peripheral nerve preparations from MBC treated hens or from negative controls. Axonal and myelinic changes were seen in histological preparations from TOTP treated hens.

It was concluded that neither Benomyl nor MBC produced neurotoxic effects in hens but that evidence of acute toxicity was seen at the highest dose levels tested with benomyl or MBC. No evidence of delayed neurotoxicity was found with Benomyl or MBC treatment, but TOTP (positive controls) did elicit such symptoms. The "no observable effect" for both parent chemical (benomyl) and metabolite (MBC) is probably around 2500 mg/kg.

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