US EPA ARCHIVE DOCUMENT

10-11-85

Tox. Chem. No. 75A - Benomyl (CFR 180.294)

004708

Acceptable Daily Intake -
EPA/ OPP / HED / Tox.

Material :

Doc. No. for Updated ADI
004708

ADI or PADI 0.05 mg/kg/day

Safety Factor = 100

Dated : 6/12/85, 4/17/85, 5/24/85

Updated : 10/4/85

Study : 3-Generation Reproduction (rat)

10/11/85
D K'edby

NOEL : 5 mg/kg

Lab. : Haskell Lab.

Study No. : 264-68

Study Date : 1968 (11/18/68)

Doc. No. : 004679

C. Fried S. Mendes
D. Bowen
Jane C. Harris Sr. Hec
10/11/85

Comments: Q* (produce hepatocellular neoplasms (M and F), and pulmonary alveolar carcinomas in male mice.)
The PADI was determined from a 3-generation rat reproduction study because it yielded the most sensitive value.
The rabbit teratology study (core grade supplementary has been identified as a data gap.

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Q* positive oncogen in mice.

75A - Benomyl

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Data Considered for Establishing an ADI , a PADI or PLD

1. 2-Year Feeding - dog (NOEL = 12.5 mg/kg ; minimum)
2. 2-Year Feeding - rat (NOEL > 125 mg/kg ; minimum)
3. Reproduction - rat (NOEL = 5 mg/kg ; minimum)
4. Teratology - rat (Teratogenic NOEL = 30 mg/kg ; microophthalmia at 67.5 mg/kg ; minimum)
5. Teratology - rabbit (Teratogenic NOEL = 15 mg/kg (HDT) ; supplementary)

Data Gap(s)

1. Teratology - rabbit

Other Data Considered

1. 2-Year Feeding/Oncogenic - mouse (positive oncogen -- increase in hepatocellular neoplasms, and pulmonary alveolar carcinomas in male)

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BQPd from a 3-Generation Rat Reproduction Study

In an effort to support the tolerances for Benomyl, a BQPd was established after a review of the tox. files. Studies considered were: 1) a 2-year rat feeding (NOEL > 125 mg/kg); 2) a 2-year dog feeding (NOEL = 12.5 mg/kg); 3) a 3-generation rat reproduction (NOEL = 5 mg/kg); 4) a rat teratology (teratogenic NOEL = 30 mg/kg); and 5) a rabbit teratology (NOEL = 15 mg/kg). The PADI was determined from a 3-generation rat reproduction study because it yielded the most sensitive value (PADI = 0.05 mg/kg; safety factor = 100).

The rabbit teratology study (can provide supplementary) has been identified as a data gap.

Benomyl, also, has been shown to produce hepatocellular neoplasms (M and F), and pulmonary alveolar carcinoma in male mice.

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation - guinea pig; Haskell lab.; 174-66; 9/28/66	technical	Acc. 105908-A MRID 00057244	no skin irritation Levels tested: 10, 25, and 40% paste	IV	004678
Dermal sensitization - guinea pig; 174-66; 9/28/66	technical	Acc. 105908-A MRID 00057244	mild sensitization		004678
Primary dermal irritation - guinea pig; 84-69; 4/18/69	technical	Acc. 050427-W MRID 00097289	mild skin irritation	IV	minimum 004679 -
Dermal sensitization- guinea pig; 84-69; 4/18/69	technical	Acc. 050427-W MRID 00097289	moderate sensitization		minimum 004679 -
Primary eye irritation - rabbit; Haskell labs; 233-72; 6/22/72	53% tech 50% WP		Mild irritation		000721 004678
90-Day feeding - rat; Haskell Lab.; #11-67; 1/31/67	70% WP (72.2% tech)	MRID 00066771	Systemic NOEL = 500 ppm LEL = 2500 ppm(incr. SGPT) dose levels: 0, 100, 500, 2500ppm(ai)		000721 004678 minimum 004679 -
90-Day feeding - dog; Haskell Lab.; #269-68; 11/20/68	51% Technical 50 % WP	MRID 00066785	Systemic NOEL = 500 ppm LEL = 2500 ppm dose levels: 0, 100, 500, 2500ppm(ai)		000721 004678 minimum 004679 -
2-Year feeding - rat; Haskell Lab.; #232-69; 8/15/69 (supp. path. report 66-77; 2/9/78)	51or72.2 % Tech 50 or 70 % WP	MRID 00097284 00068981	Systemic NOEL > 2500 ppm No effect on sperm production Dosage levels = 100, 500, 2500 ppm		000721 004678 minimum 004678 -

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-Year feeding - dog; Haskell Lab.; #48-70 (129-69,74-77); 3/7/70	51or72.2 % Tech 50 or 70 % WP	MRID 00097305 00081913 00097318 00097326 00061618	Systemic NOEL = 500 ppm Systemic LEL = 2,500 ppm (HDT, cirrhosis and adverse effects on testis. No effect on sperm production Dosage levels = 100, 500, 1500, 2500 ppm		000721 004678 minimum 004679 -
3-Generation reproduction - rat; Haskell Lab.; #264-68; 11/18/68	51or72.2 % Tech 50 or 70 % WP		Systemic NOEL = 100 ppm LEL = 500 ppm levels tested:0, 100, 500, 2500 ppm(ai)		000721 004678 minimum 004679 -
Teratology - rabbit; Hazleton Lab.; #NRD-1079; 1968	53.5% WP		Terata NOEL = 500 ppm (HDT) NOEL fetal, maternal toxicity > 500 ppm Levels tested: 0, 100, 500 ppm diet		000722 Supplementary 000723
Teratology - rat; Haskell Lab.; #286-70; 1970	53.5% WP		Terata NOEL = 5,000 ppm (HDT)		000722
Teratology - rat; Shtenberg & Torchinsky; 1972	Technical		Fetotoxic NOEL = 62.5 mg/kg Fetotoxic LEL = 125 mg/kg Terata NOEL = 62.5 mg/kg Terata LEL = 125 mg/kg (Brain hernias, hydrocephaly and microphtalmia) Dosage = 62.5, 125, 250, 500 mg/kg (gavage)		000722
51-Week feeding - mice; Haskell Lab.; #539-78; 10/13/78	INT-1991	236765	Study terminated after 51 weeks due to high morbility and mortality in all groups (systemic bacterial infection) Levels tested = 0, 500, 1500, 5000 and 7000 ppm		Supplementary 000723
Acute oral LD_{50} - rat; Haskell;#421-80;5/23/80	Benomyl - 75% (Benlate DF)	243043	LD_{50} > 5000 mg/kg	IV	Guideline 000863

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Tox Chem No. 75A - Benomyl

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute dermal LD_{50} - rabbit; Haskell; #554-80, 7/23/80	Benomyl - 75% (Benlate DF)	243043	LD_{50} > 2000 mg/kg Severe skin irritation.	III	Guideline 000863
Primary eye irritation - rabbit; Haskell; #497-80; 6/13/80	Benomyl - 75% (Benlate DF)	243043	Corneal opacity at 8 days. For the irrigated eyes, irritation cleared by day 8.	II	Guideline 000863
Primary dermal irritation - rabbit; Haskell; #367-80;5/12/80	Benomyl - 75% (Benlate DF)	243043	Slight edema and slight erythema at 24 hours; at 72 hours, only very slight erythema. All scores were Ø by day 6.	IV	Guideline 000863
Teratology - rat; Haskell Labs.; report #587-82; E.I. DuPont de Nemours; 1982	Technical 99.1% Pure	248563 249749	STUDY LIMITED TO MICROPHTHALMIA NOEL = 30 mg/kg LEL = 62.5 mg/kg (microphthalmia) Levels tested by gavage - (0, 3, 6.25, 10, 20, 30 & 62.5)		Supplementary 002578 Upgraded to Minimum 003042
2 Year feeding - mouse; Dupont Haskell Lab; 20-80; 1/26/82	Benomyl 99-99.2% pure	MRID 00096514	Onocgenic NOEL < 500 ppm male and female, significant increase in hepatocellular neoplasms in male and female, pulmin. alveol. carcin. males, degen. of testes and epid. at 5000 ppm. Dosage levels = 500, 1500, 5000 ppm (5000 lowered from 7500 ppm)		003726 minimum 004679 -
Teratology - rat; Sherman et al.; 1975	Benomyl		Terata NOEL = 400 mg/kg (HDT) (inconclusive result since ingested dose not measured accurately)		003728
Teratology - rat; Midwest Res. Inst.; 1979	Benomyl		Terata NOEL < 62.5 mg/kg (LDT; CNS herniations, defects of extremities, lack of eye bulges) Dosage levels = 0 - 500 mg/kg/day by gavage		003728

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results	TOX Category	CORE Grade
Acceptable Daily Intake EPA/OPP/HED/TOX	Sanomyl		PADI = .05 mg/kg/day Safety factor = 100 Dated: Study: 3-Generation Reproduction Study (rat) NOEL: ~~5 mg~~ 100ppm or 5mg/kg/day Lab: Haskell Lab. Factor. Ind. Med. Study No. Haskell # 264-68 (11-67) Study Date 9/13/68 Doc. No. 004678 Oncogenic potential - positive.		~~[illegible]~~ (Lox#) Ng. Std.

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Benomyl 6/12/85

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File last updated 6/12/85

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NOEL change not recorded

ACCEPTABLE DAILY INTAKE

RAT, Older mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	HPI mg/day(60kg)
5.000	100.00	100	0.0500	3.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Pineapple(123)	35.000	0.30	0.15560
Apricots(3)	15.000	0.11	0.02529
Cherries(30)	15.000	0.10	0.02299
Nectarines(100)	15.000	0.03	0.00675
Peaches(114)	15.000	0.90	0.20235
Plums,inc prunes(125)	15.000	0.13	0.02989
Citrus Fruits(33)	10.000	3.81	0.57179
Grapes, not raisins(67)	10.000	0.45	0.06745
Raisins(134)	50.000	0.04	0.03066
Mushrooms(97)	10.000	.03	0.00450
Blackberries(15)	7.000	0.03	0.00315
Blueberries(16)	7.000	0.03	0.00315
Boysenberries(17)	7.000	0.03	0.00315
Dewberries(52)	7.000	0.03	0.00315
Loganberries(86)	7.000	0.03	0.00315
Raspberries(135)	7.000	0.03	0.00315
Apples(2)	7.000	2.53	0.26565
Pears(116)	7.000	0.26	0.02683
Rice(137)	5.000	0.55	0.04139
Strawberries(152)	5.000	0.18	0.01380
Tomatoes(163)	5.000	2.87	0.21561
Celery(28)	3.000	0.29	0.01288
Mangoes(86)	3.000	0.03	0.00135
Beans(9)	2.000	2.04	0.06120
Bananas(7)	0.200	1.42	0.00426
Avocados(6)	3.000	0.03	0.00135
Cucumbers,inc pickl(46)	1.000	0.73	0.01088
Melons(92)	1.000	2.00	0.03005
Pumpkin,inc squash(131)	1.000	0.11	0.0169
Summer squash(155)	1.000	0.03	0.00045
Wintersquash(171)	1.000	0.03	0.00045
Peanuts(115)	0.200	0.36	0.00107
Soybeans (oil)(146)	0.200	0.92	0.00275
Sugar,canebeet(154)	0.200	3.64	0.01091
Nuts(101)	0.200	0.10	0.00031
Eggs(54)	0.100	2.77	0.00416
Meat,inc poultry(89)	0.100	13.55	0.02077
Corn,sweet(40)	0.200	1.43	0.00429
Sweet Potatoes(157)	0.200	0.40	0.00120
Eggplant(53)	0.200	0.03	0.00009
Peppers(120)	0.200	0.12	0.00037
Broccoli(19)	0.200	0.10	0.00031
Cauliflower(27)	0.200	0.07	0.00021
Chinese Cabbage(177)	10.000	0.03	0.00450
Collards(37)	0.200	0.08	0.00025
Garlic(61)	0.200	0.03	0.00009

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Tolerance Reassessment

Tolerances for benomyl in the CFR § 180.294 are for the parent compound and its metabolites containing the benzimidazole moiety (calculated as benomyl).

ADI

The five studies required to determine an acceptable daily intake (ADI) are listed in table 1.

Table 1. 5 required studies and NOELs for establishing an ADI

Study Type	NOEL ppm	NOEL mg/kg/day	Reference
chronic rat feeding	2500	125	00097284, 00068981
chronic dog feeding	500	37.5	00097305, 00081913, 00097318, 00097326, 00061619
2 generation reproduction	100	5	00066773
rat teratology		30	acc# 256575
rabbit teratology	not determined*		00035352

The provisional ADI (PADI) was determined, rather than an ADI, because one of the required studies is absent. The no observable effect level (NOEL) of 5 mg/kg/day, obtained from the most sensitive study (see table 1), was divided by a safety factor of 100 to derive a PADI of 0.05 mg/kg/day. The P maximal permissable intake (PMPI) for a 60 kg adult is (0.05 mg/kg/day x 60 kg) 3 mg/day.

TMRC

Tolerances for the commodities in table 2 have been published in the federal register and have a theoretical maximal residual concentration (TMRC) of 1.9785 mg/day of benomyl which is 65.78 % of the PADI. The TMRC of 1.9785 mg/day would be 0.03298 mg/kg/day for a 60 kg adult. Table 2 lists commodities that have petitions pending for tolerances. These commodities, if approved, would add 0.2729 mg/day, raising the TMRC 13.83 % to 2.2464 mg/kg, which is 74.88 % of the PADI. The new TMRC of 2.2464 mg/day would be 0.03733 mg/kg/day for a 60 kg adult. The proceeding calculations used the worst case for dietary exposure and did not consider per cent of crop treated and actual residue values (including processing) in to account.

The PD 4 lists percent of crop treated where the data is available (see table 2). When these values are taken into consideration the average residue levels of benomyl in the diet, decrease to 1.00689 mg/day which is 33.56 % of the PADI.

A 3C2B letter of May 14, 1985, required real residue on apples, peaches pineapples rice milk soybeans citrus and tomatoes. These commodities comprise 65 % of the TMRC. The resultant residue data may further decrease the % ADI, teratagenic, spermatogenic and oncogenic risks from benomyl.

*study is core-supplementary

~~No CFR Number~~ 180.294 Benomyl 10/17/85

File last updated 10/17/85

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ACCEPTABLE DAILY INTAKE DATA

RAT,Older mg/kg	NOEL ppm	S.F.	PADI mg/kg/day	PMPI mg/day(60kg)
5.000	100.00	100	0.0500	3.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Pineapple(123)	35.000	0.30	0.15560
[illegible]ricots(3)	15.000	[illegible]	[illegible]
Cherries(30)	15.000	0.10	0.02299
[illegible](100)	15.000	0.03	[illegible]
[illegible]eaches(114)	15.000	0.90	0.20235
Plums,inc prunes(125)	15.000	0.13	0.02989
Citrus Fruits(33)	10.000	3.81	0.57179
Grapes, not raisins(67)	10.000	0.45	0.06745
Raisins(134)	50.000	0.04	0.03066
Mushrooms(97)	10.000	0.03	0.00450
Blackberries(15)	7.000	0.03	0.00315
Blueberries(18)	7.000	0.03	0.00315
Boysenberries(17)	7.000	0.03	0.00315
Dewberries(52)	7.000	0.03	0.00315
Loganberries(86)	7.000	0.03	0.00315
Raspberries(135)	7.000	0.03	0.00315
Apples(2)	7.000	2.53	0.26565
Pears(116)	7.000	0.26	0.02633
Rice(137)	5.000	0.55	0.04139
Strawberries(152)	5.000	0.18	0.01380
Tomatoes(163)	5.000	2.87	0.21561
Celery(28)	3.000	0.29	0.01288
Mangoes(88)	3.000	0.03	0.00135
Beans(5)	2.000	2.04	0.06120
Bananas(7)	0.200	1.42	0.00426
Avocados(6)	3.000	0.03	0.00135
Cucumbers,inc picki(46)	1.000	0.73	0.01088
Melons(92)	1.000	2.00	0.03005
Pumpkin,inc squash(131)	1.000	0.11	0.00169
Summer Squash(155)	1.000	0.03	0.00045
Wintersquash(171)	1.000	0.03	0.00045
Peanuts(115)	0.200	0.36	0.00107
[illegible](148)	0.200	0.92	0.00275
Sugar,cane&beet(154)	0.200	3.64	0.01091
Nuts(101)	0.200	0.10	0.00031
Eggs(54)	0.100	2.77	0.00416
Meat,inc poultry(69)	0.100	13.85	0.02077
Corn,sweet(40)	0.200	1.43	0.00429
Sweet Potatoes(157)	0.200	0.40	0.00120
Eggplant(53)	0.200	0.03	0.00009
Peppers(120)	0.200	0.12	0.00037
Broccoli(19)	0.200	0.10	0.00031
Cauliflower(27)	0.200	0.07	0.00021
Chinese Cabbage(177)	10.000	0.03	0.00450
Collards(37)	[illegible]	[illegible]	[illegible]
Garlic(61)	0.200	[illegible]	0.00009

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Kale(75)	0.200	0.03	0.00009
Kohlrabi(76)	0.200	0.03	0.00009
Mustard Greens(95)	0.200	0.06	0.00018
Spinach(150)	0.200	0.05	0.00015
Rutabagas(139)	0.200	0.03	0.00009
Cabbage,sauerkraut(22)	0.200	0.74	0.00221
Liver(211)	0.200	0.03	0.00009
Milk&Dairy Products(93)	0.100	28.62	0.04292
Carrots(24)	0.200	0.48	0.00144
Currants(48)	7.000	0.03	0.00315
Papayas(109)	3.000	0.03	0.00135
Dandelion(194)	10.000	0.03	0.00450
Turnips(165)	0.200	0.05	0.00015
Turnip Greens(166)	6.000	0.03	0.00270
Brussel Sprouts(20)	15.000	0.03	0.00675
Barley(8)	0.200	0.03	0.00009
Oats(102)	0.200	0.36	0.00107
[redacted](140)	0.200	[redacted]	[redacted]
Wheat(170)	0.200	10.36	0.03109

[redacted]

PMPI	TMRC	%PADI
3.0000 mg/day(60kg)	1.9735 mg/day(1.5kg)	65.78

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Unpublished,Tox Approved 9E2136,6F1810,2007,2866

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Yams(Yautia)(199)	0.200	0.03	0.00009
Lettuce(84)	10.000	1.31	0.19622
Eggplant(53)	4.800	0.03	0.00216
Peppers(120)	4.800	0.12	0.00833
Escarole/endive(56)	10.00	0.03	0.00450

PMPI	TMRC	%PADI
3.0000 mg/day(60kg)	2.1853 mg/day(1.5kg)	72.84

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