US EPA ARCHIVE DOCUMENT

TOXR 004785 Doc # 004785

3-25-86

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Benomyl

CAS #: 17804-35-2
Caswell #: 75A

Carcinogenicity: Evidence of oncogenicity in mice, no evidence in rats. Classified as a Category C oncogen

Systemic Toxicity: See below.

Preparation Date: 3/5/86

Endpoint	Experimental Doses	UF	MF	RfD
Haskell Lab. for Toxicology and Industrial Medicine (1968) 3-Generation Reproduction Rat Study	5 mg/kg/day NOEL 25 mg/kg/day LEL	100	-	0.05 mg/kg/day (ADI)

Decreased pup weight

Conversion factor (rat) 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

3-Generation Reproduction Rat Study
Haskell Laboratory for Toxicology and Industrial Medicine, Report No. 264-68(11-67), November 18, 1968

Benomyl 50 or 70% WP (dose based on % a.i.) was administered in the diet at 0, 100, 500, and 2500 ppm to male and female ChR-CD rats for 3 generations (7 litters). Six males and females were mated for the first generation, 12 males and females for the second generation, and 20 males and females for the third generation. No treatment related effects were seen with the exception of decrease in pup weanling weight at 500 ppm.

1 of 19

Uncertainty Factors (UFs):

A UF of 100 includes uncertainties in extrapolation from laboratory animals to humans. The extrapolation from the teratology data was considered to be sufficiently covered by this UF, since the NOEL for teratogenic effects is 30 mg/kg/day i.e. 6 times higher than the NOEL of 5 mg/kg/day used to establish the RfD. Thus, there is an overall 600 fold margin between the teratogenic NOEL and the RfD.

Modifying Factors (MFs):

None

Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding - Dog (NOEL=12.5 mg/kg; LEL=62.5 mg/kg, cirrhosis and body weight depression; minimum)

2) 3-Generation Reproduction - Rat (Systemic NOEL=5 mg/kg; LEL=25 mg/kg, decreased pup weight; minimum)

3) Teratology - Rat (Terata NOEL=30 mg/kg; Terata LEL=62.5 mg/kg, microphthalmia; minimum)

4) Teratology - Rabbit (Maternal and Fetotoxic NOEL $\geq$500 ppm (HDT); supplementary)

5) 2-Year Feeding/Oncogenic - Rat (Systemic NOEL >125 mg/kg; minimum)

6) 90-Day Feeding - Dog (NOEL=12.5 mg/kg; LEL=62.5 mg/kg, increase SGPT and alkaline phosphatase; minimum)

Data Gap(s)

None

Other Data Considered

1) 2-Year Feeding/Oncogenic - Mice (Positive oncogen, NOEL <75 mg/kg, hepatocellular neoplasms, and pulmonary alveolar carcinoma in males; no core grade)

Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The critical study appears to be of good quality and is therefore given medium confidence. Since additional studies are of good to fair quality, the RfD is given medium confidence.

Documentation of RfD and Review:

Registration Standard April, 1986
Special Review Position Document

Agency RfD Review:

First Review: 3/25/86
Second Review:
Verification Date: 3/25/86

U.S. EPA Contact:

Primary: George Ghali FTS 557-4382

Secondary: Marion Copley FTS 557-1511

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

004785

Acceptable Daily Intake - EPA/ OPP / HED / Tox. (ADI update)

Material : Benomyl

Doc. No. for Updated ADI

ADI or PADI .05 mg/kg/day

004785

Safety Factor = 100

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

Updated : 12/4/85

Study : 3-Generation Reproduction (Rat)

NOEL : 5 mg/kg

Lab. : Haskell Lab

Study No. : 264-68

Study Date : 1968 (11/18/68

Doc. No. : 004679

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Comments:

Requests to change PADI to ADI, the ~~require~~ data gap of a rabbit teratology study has been satisfied by: Teratology - mouse - gavage (Doc. #004679)

Core-classification: minimum

Teratogenic NOEL = 50 mg/kg

LEL = 100 mg/kg (supra occipital scars, subnormal vertebral centrum, supernumerary ribs and cleft palate.)

maternal NOEL : 200 mg/kg (HDT)

004785 G. Gnale

004765

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Benomyl

CAS #: 17804-35-2

Carcinogenicity: Heptacellular carcinomas in mice

Caswell #: 75A

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Haskell Lab. for Toxicology and Industrial Medicine (1968) 3-Generation Reproduction Rat Study Decreased pup weight	5 mg/kg (NOEL) 25 mg/kg (LEL)	100	-	0.05 mg/kg/day (ADI)

Endpoint and Experimental Doses:

3-Generation Reproduction Rat Study
Haskell Laboratory for Toxicology and Industrial Medicine, Report No. 264-68(11-67), November 18, 1968

Benomyl 50 or 70% WP (dose based on % a.i.) was administered in the diet at 0, 100, 500, and 2500 ppm to male and female ChR-CD rats for 3 generations (7 litters). Six males and females were mated for the first generation, 12 males aand females for the second generation, and 20 males and females for the third generation. No treatment related effects were seen with the exception of decrease in pup weanling weight at 500 ppm.

Preparation Date: 3/5/86

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004785

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Industrial Medicine, Report No. 264-68(11-67),
November 18, 1968

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Preparation Date: 3/5/86

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Uncertainty Factors (UFs):

A UF of 100 includes uncertainties in extrapolation from laboratory animals to humans. The extrapolation from the teratology data was considered to be sufficiently covered by this UF (600 fold MOS).

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Modifying Factors (MFs):

None

.....

Additional Comments:

Data Considered for Establishing a ADI, PADI or PLD

1) 2-Year Feeding - Dog (NOEL=12.5 mg/kg; LEL=62.5 mg/kg, cirrhosis and body weight depression; minimum)

2) 3-Generation Reproduction - Rat (Systemic NOEL=5 mg/kg; LEL=25 mg/kg, decreased pup weight; minimum)

3) Teratology - Rat (Terata NOEL=30 mg/kg; Terata LEL=62.5 mg/kg, microphthalmia; minimum)

4) Teratology - Rabbit (Maternal and Fetotoxic NOEL $\geq$500 ppm (HDT); supplementary)

5) 2-Year Feeding/Oncogenic - Rat (Systemic NOEL >125 mg/kg; minimum)

6) 90-Day Feeding - Dog (NOEL=12.5 mg/kg; LEL=62.5 mg/kg, increase SGPT and alkaline phosphatase; minimum)

Data Gap(s)

None

Other Data Considered

1) 2-Year Feeding/Oncogenic - Mice (Positive oncogen, NOEL <75 mg/kg, hepatocellular neoplasms, and pulmonary alveolar carcinoma in males; no core grade)

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Study: Medium Data Base: Medium RfD: Medium

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Documentation of RfD and Review:

.....

Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary: George Ghali

Secondary:

00478

STUDY TYPE: Reproduction study - rats TOX. CHEM. NO.: 75A

HASKELL LAB. REPORT NUMBER: 264-68(11-67) FICHE/MASTER: 00066773
MR NO.: 966

SPONSOR: E. I. du Pont de Nemours and Company

STUDIES PERFORMED AT: Haskell Lab. for Toxicology and Industrial Medicine, Wilmington, Del.

§ AUTHORS: H. Sherman

§ DATE REPORT SUBMITTED: November 18, 1968

TEST MATERIAL: Benomyl, 50 or 70% wettable powder; 1-(Butylcarbamoyl 2-benzimidazolecarbamic acid, methyl ester; (72.2%† or 51.5-52.0%†† tech.)

SYNONYMS: Carbamic Acid, (1-((Butylamino)-carbonyl)-1H-benzimidazol-2-yl)-methyl ester
INT-1991
NB- 5409-91
DPX-3866
N.B. 8084-1668

" Reproduction study

Rat, 3-generation, 7-litter.

No. of Animals. 6 M and 6 F/group, F_0 parents (animals left from 90-day study); 12 M and 12 F/group, F_{1b} parents; and 20 M and 20 F/group, F_{2b} parents.

Feeding Levels.* 0, 100, 500, and 2,500 ppm.
Duration. Time to produce 3 generations, 7 litters in all.
Mortality. No effect on numbers of stillborn or on survival to 4 days or to weaning.
Body Weight. Pups from parents at 500 and 2,500 ppm weighed less, at weaning, than control or "100-ppm" pups in the F_{2b}, F_{3a}, F_{3b}, and F_{3c} litters. (See Table, below.) However, the various groups of F_{3c} pups kept on test for 9 weeks post-weaning and for a further 6 weeks on control diets had growth curves of similar slope.
Histopathology. No effect on F_{3b} weanlings. Tissues studied were: Pituitary, thyroid, parathyroid, adrenal, skeletal muscle, sciatic nerve, brain, spinal cord, eye, exorbital lacrimal gland, mammary gland, bone marrow, spleen, thymus, lung, upper trachea, heart, stomach, duodenum, cecum, salivary gland, pancreas, liver, testis or ovary, epididymus or fallopian tube, uterus or prostate, urinary bladder, and kidney.
"No-Effect Level." Conservatively, 100 ppm; since average weanling weights in F_{2b}, F_{3a}, F_{3b}, and F_{3c} litters are low for "500-ppm" and "2,500-ppm" pups, as compared to corresponding control and "100-ppm" values.

March 25, 1970
M. Quaife, Ph.D.

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§ Information obtained from the WHO bibliography (Nov.-Dec./83) on Benomyl.
† used through week 10 of the F_{1B} generation
†† used for the remainder of the reproduction

Table from original review:

PP Nos. OFO-906
and OGO-936 -8- March 25, 1970

Parameters in this reproduction study are tabulated:

ppm Benomyl	Average Litter Size	Average No. Born Alive	F.I. (%)	G.I. (%)	V.I. (%)	L.I. (%)	Average Weanling Weight (g)
			F_{1a} Litter				
0	11.7	11.2	100	100	94	98	48
100	11.2	11.2	67	100	100	100	54
500	10.2	10.0	83	100	98	98	59
2,500	13.0	12.8	100	100	97	93	57
			F_{1b} Litter				
0	12.5	10.8	100	100	87	98	57
100	13.6	13.2	83	100	97	100	58
500	11.6	10.6	83	100	91	93	62
2,500	13.2	12.[illegible]	100	100	91	100	54
			F_{2a} Litter				
0	10.8	10.4	83	100	95	96	51
100	11.8	11.6	92	100	97	95	56
500	10.6	10.5	83	100	98	97	52
2,500	11.3	11.2	91	100	96	98	48
			F_{2b} Litter				
0	10.8	10.0	92	91	90	99	60
100	13.6	13.6	92	100	100	100	59
500	11.1	10.6	67	100	89	97	52
2,500	12.9	12.6	91	90	96	100	51
			F_{3a} Litter				
0	9.5	8.9	85	100	93	99	56
100	11.3	10.7	75	93	90	98	57
500	9.6	9.5	70	100	98	100	52
2,500	11.9	11.7	80	100	98	99	51
			F_{3b} Litter				
0	13.1	12.6	80	100	95	99	58
100	13.5	13.3	68	92	97	100	59
500	11.1	10.7	70	100	94	99	52
2,500	11.9	10.4	85	100	84	98	54
			F_{3c} Litter				
0	11.6	10.0	65	92	87	100	60
100	11.9	10.5	67	100	87	100	62
500	9.5	8.5	55	100	88	93	52
2,500	13.0	10.6	75	93	79	96	51

Addendum to review for clarification of material and methods by M. Copley.

Dietary levels of INT-1991 (using 50% WP):

Group	Treatment
Control (I)	food + 1% CO
Low dose (V)(LDT)	food + 1% CO + 100 ppm INT-1991 (0.01% formulation)
Mid dose (VI)(MDT)	food + 1% CO + 500 ppm INT-1991 (0.05% formulation)
High dose (VII)(HDT)	food + 1% CO + 2500 ppm INT-1991 (0.25% formulation)

CO - corn oil

Species: ChR-CD rats.
Mating procedure: Each F_0 female was exposed sequentially to 3 F_0 males (from the same dietary group) for 5 days. After mating (15 da total) the females were separately housed and examined twice daily till parturition.

F_{1A} were sacrificed at weaning.
F_{1B} - Twelve males and females from each group were mated at 3 months.
F_{2A} were sacrificed at weaning.
F_{2B} - Twenty males and females from each group were mated at 3 months
F_{3A} were sacrificed at weaning.
F_{3B} - Two of each sex from each of five litters/group were examined at necropsy. Those from the control and HDT were examined histologically.

F_{3C} - used for reassessment of growth curve.

All litters were reduced to 10 when necessary. Parameters measured were: No. of pregnancies; no. of survivors at birth, 4, 12 and 21 days; body weight at weaning (21 days).

CONCLUSION: NOEL = 100 ppm
LEL = 500 ppm (decrease in pup weights)

CORE-CLASSIFICATION: core minimum

Original review evaluated and addendum added by M.P.Copley, D.V.M.
Tox. Br.
9/12/85

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	50% WP		LD_{50} > 10,000 mg/kg	III	000721
Acute inhalation LC_{50} - rat	50% WP		LC_{50} > 2.0 mg/L	III	000721
Acute inhalation LC_{50} - rat	Technical		LC_{50} > 1.37 mg/L	II	000721
Acute inhalation LC_{50} - rat; Hazleton Lab; #201-220; 10/18/68	50% a.i.		LC_{50} > 4.01 mg/L (HDT; testicular alterations noted at all levels tested: 0.27, 1.0 and 4.01 mg/L)	III	000721
Primary dermal irritation - guinea pig	50% WP		Mild irritation		000721
Dermal sensitization - guinea pig	50% WP		Mild sensitization		000721
Primary eye irritation - rabbit	53% a.i.		Mild irritation		000721
90-Day feeding - rat; Haskell Lab.; #11-67; 1/31/67	Technical		Systemic NOEL = 500 ppm		000721
90-Day feeding - dog; Haskell Lab.; #269-68; 11/20/68	Technical		Systemic NOEL = 500 ppm		000721
2-Year feeding - rat; Haskell Lab.; #232-69; 8/15/69	Technical		Systemic NOEL > 2500 ppm No effect on sperm production Dosage levels = 100, 500, 2500 ppm		000721

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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.
2-Year feeding - dog; Haskell Lab.; #48-70; 3/7/70	Technical		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
3-Generation reproduction - rat; Haskell Lab.; #264-68; 11/18/68	Technical		Systemic NOEL = 100 ppm		000721
Teratology - rabbit; Hazleton Lab.; #MRD-1079; 1968	53.5% WP		Terata NOEL = 500 ppm (HDT)		000722
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%	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%	243043	LD_{50} > 2000 mg/kg Severe skin irritation.	III	Guideline 000863
Primary eye irritation - rabbit; Haskell; #497-80; 6/13/80	Benomyl - 75%	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%	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
t Teratology - rat; Haskell Labs.; report #587-82; E.I. DuPont de Nemours; 1982	Technical 99.1% Pure	248563 249749	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; 1982	Benomyl		Onocgenic NOEL < 500 ppm male and female significant increase in hepatocellular neoplusms in male and female Dosage levels = 500, 1500, 5000 ppm		003726
t Teratology - rat; Shernian et al.; 1975	Benomyl		Terata NOEL = 400 mg/kg (HDT) (inconclusive result since ingested dose not measured accurately)		003728
t 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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Tox Chem No. 75 A Benomyl

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade Doc. No.
Teratology - mice; Health Effects Res. Lab; US EPA; 1979	Benomyl		Terata NOEL < 200 mg/kg (LDT; increased resorptions, decreased litter size; herniations; reduction of extremities Dosage levels = 200 and 400 mg/kg by gavage		003728
Teratology - rat; Health Effects Res. Lab; US. EPA; 1980	Benomyl		Terata NOEL = 31.2 mg/kg Terata LEL = 62.5 mg/kg (microphthalmia and increased fetal mortality; reduced fetal weight) Dosage levels = 15.6, 31.2, 62.5 and 125 mg/kg by gavage		003728
Teratology - rat; Health Effects Res. Lab; US EPA; 1980	Benomyl		NOEL = 169 mg/kg LEL = 298 mg/kg (weight change) No dose related incidences of anomalies or malformations Dosage levels = 0 - 500 mg/kg in diet		003728
Post natal teratology - rat; health Effects Res. Lab; US EPA; 1980	Benomyl		Benomyl was administered by gavage to dams from day 7 of gestation to day 15 of lactation Fetotoxic NOEL = 31.2 mg/lg Fetotoxic LEL = 62.5 mg/kg (decreased weight of testes, ventral prostate, and seminal vesicles)		003728
Teratology - rat; Haskell Lab; #649-80; 1980	Benomyl		Unilateral microphthalmia at 10 mg/kg/day (2 animals) NOEL = 30 mg/kg LEL = 62.5 mg/kg (embryotoxicity) Dosage levels - 0, 3, 10, 62.5, 125 mg//kg/day by gavage		003728

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Tox Chem No. 75 A

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
24-Day feeding - rat; Carter and Laskey; 1982	Benomyl		Dose levels = 0, 200, 400 mg/kg/day for 10 days. Animals sacrificed 14 days later Depression of sperm count and decreased caudal epididymis weights at 200 mg/kg		003744
1-Generation reproduction - rat; Kavlock et al; 1982	Benomyl		NOEL = 15.6 mg/kg LEL = 31.2 mg/kg (decrease testicular weights in offspring) Material given by gavage during gestation and lactation		003744
Teratology - mice; Kavlock et al; 1982	Benomyl		Dosage levels=0, 50, 100, 200 mg/kg given by gavage NOEL = 50 mg/kg LEL = 100 mg/kg (supra occipital scars, subnormal vertebral centrum, supernumerary ribs)		003744
Teratology - rat; Kavolck et al; 1982	Benomyl		Dosage levels = 0, 125 and 500 mg/kg /day (calculated dose in diet) Terata NOEL > 500 mg/kg (HDT)		003744
Spermatogenic - rat; Sherman and Krauss; 1966	Benomyl		Degeneration of germinal tissue and aspermatogenesis at 3400 mg/kg(LDT)		003744
Acute spermatogenic - rat; Sherman; 1965	Benomyl		Reduction of sperm at 670 mg/kg (single dose used)		003744
10-Day spermatogenic - rat; Sherman and Kraus; 1966	Benomyl		NOEL < 200 mg/kg(single dose tested)		003744

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Caswell #: 75A

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Modifying Factors (MFs):

None

Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding - Dog (NOEL=12.5 mg/kg; LEL=62.5 mg/kg, cirrhosis and body weight depression; minimum)

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Data Gap(s)

None

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Other Data Considered

1) 2-Year Feeding/Oncogenic - Mice (Positive oncogen, NOEL <75 mg/kg, hepatocellular neoplasms, and pulmonary alveolar carcinoma in males; no core grade)

Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

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Documentation of RfD and Review:

Registration Standard April, 1986
Special Review Position Document

Agency RfD Review:

First Review: 3/25/86
Second Review:
Verification Date: 3/25/86

U.S. EPA Contact:

Primary: George Ghali FTS 557-4382

Secondary: Marion Copley FTS 557-1511

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