

## Dimethipin; CASRN 55290-64-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

### STATUS OF DATA FOR Dimethipin

**File First On-Line 01/31/1987**

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	05/01/1990
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Dimethipin  
CASRN — 55290-64-7  
Primary Synonym — Harvade  
Last Revised — 05/01/1990

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an

elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased absolute and relative liver weight	NOEL: 40 ppm (2 mg/kg/day)	100	1	2E-2 mg/kg/day
2-Year Rat Feeding Study	LEL: 200 ppm (10 mg/kg/day)			
Uniroyal Chemical Co., 1981a				

\*Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

### I.A.2. Principal and Supporting Studies (Oral RfD)

Uniroyal Chemical Company. 1981a. MRID No. 00145225. Available from EPA. Write to FOI, EPA, Washington DC 20460.

Harvade was fed to albino rats (50/sex/group at initiation) at levels of 40, 200, and 1000 ppm (2, 10, and 50 mg/kg/day) (Groups 2, 3, 4, respectively). A fourth group of rats (Group 1) received only the basal diet and served as the control group. After 104 weeks on study (that is, week 105 and 106) all of the surviving rats were sacrificed. Criteria used for evaluation of compound effect were mortality, clinical signs, body weights, food consumption, incidences of suspect neoplasms, organ weights and gross microscopic pathology.

No treatment-related clinical signs or neoplasms were noted during the study. There was good correlation between gross and microscopic findings. At 104 weeks, low- and mid-dose groups had survival rates comparable to controls. During the first 51 weeks, body weight decreases were noted in high-dose group. Body weight gain among groups was comparable for the remainder of the study. Absolute and relative liver weights were higher in the male low- and high-dose and

significantly higher in the female mid-dose group. Liver weight was also increased in the mid-dose male group and female high-dose group. Histologically, there was an increased incidence of focally dilated bile ducts containing basophilic homogeneous material (this finding represents partial or complete inhibition of normal bile flow in the liver) in the mid- and high- dose groups. Control and low-dose rats showed this effect to a lesser degree.

The NOEL for this study is 40 ppm (2 mg/kg/day) based on increased absolute and relative liver weight observed at 200 ppm (10 mg/kg/day).

### **I.A.3. Uncertainty and Modifying Factors (Oral RfD)**

UF — An uncertainty factor of 100 was used to account for the inter- and intraspecies differences. Although the LEL in the chronic dog study was 7.5 mg/kg/day (LDT), an additional uncertainty factor was not felt necessary since the observed effects were marginal and not dose related.

MF — None

### **I.A.4. Additional Studies/Comments (Oral RfD)**

Data Considered for Establishing the RfD

1) 2-Year Feeding (oncogenic) - rat: Principal study - see previous description; core grade minimum (Uniroyal Chemical Co., 1981a)

2) 1-Year Feeding - dog: Dietary levels tested: 0, 300, 1000, and 3000 ppm (0, 7.5, 25, and 75 mg/kg/day); Groups of 6 male and 6 female purebred beagle dogs were given diets ad libitum for 1 year. Toxic signs of thinness and decreased activity were noted for most dogs at 3000 ppm and one female dog at 1000 ppm. One male and three female dogs of the 3000 ppm group died or were sacrificed moribund during the study. Body weight of female dogs at 3000 ppm was significantly decreased in comparison to controls. Male body weights of the 3000 ppm group were significantly decreased at 13 and 26 weeks and also decreased during other times of the study. The body weights of the 300 and 1000 ppm male and female groups were comparable to controls. Mean food consumption of the 3000 ppm male and female dogs was decreased in comparison to controls during most of the study. Erythrocytes, hemoglobin, and hematocrit were significantly reduced in the 3000 ppm male and female dogs. Platelets for the high-dose dogs were significantly elevated during most of the study. Testicular degeneration was noted in the following pattern: 0 ppm, 0/6; 300 ppm, 2/6; 1000 ppm, 1/6; 3000 ppm, 3/6. Histological effects in the testes included multinucleation of spermatocytes, sperm stasis, atrophy, mineralization, and epithelial cell degeneration of the seminiferous tubules. These changes were not dose-related

with respect to number or severity. the relative weight of testes was significantly increased in the 3000 ppm male dogs. Also observed microscopically was a chronic interstitial nephritis among males at terminal sacrifice which occurred in the following manner: 0 ppm, 0/6; 300 ppm, 0/6; 1000 ppm, 3/6; 3000 ppm, 2/6. The LEL for systemic toxicity is equal to or less than 300 ppm (7.5 mg/kg/day), the lowest dose tested. Therefore a NOEL for systemic toxicity was not established; core grade minimum (Uniroyal Chemical Co., 1981b)

3) 2-Generation Reproduction - rat: Dietary levels tested: 0, 50, 200, and 800 ppm (0, 2.5, 10, and 40 mg/kg/day); Groups of 15 male and 25 female CD (SD) BR weanling rats received diets containing dimethipin for 106 days when the F1a litters were produced. Breeding of the F1b litters were initiated 14 days after the last F1a litter had been weaned. Weanling animals of the F1b litter were selected as parents for the F2a and F2b litters. Significant decreases in body weight for the 800 ppm females were noted between weeks 0 through 17 of the growth period. Food consumption of HDT males during the growth period was significantly reduced at week 9. Food consumption for HDT females was significantly reduced from weeks 6 through 9 and weeks 11 through 17. In addition, the food consumption of the 200 ppm females was significantly decrease at week 6. Significant decreased in body weight for the HDT non-pregnant F1b females were observed on weeks 25 through 27 of the reproductive phase. Dam body weight during F2a gestation was significantly decreased on days 0, 7, 14, and 20 at the HDT. Dam body weight during lactation was significantly reduced at days 0 and 14 at the HDT. Pup weight gain for the F2a litters was significantly decreased at day 21 at the HDT. Dam body weight weight during the F2b gestation was significantly decreased at days 0, 7, 14, and 20. Dam body weight during the F2b lactation was significantly decreased on days 0 and 7. Pup weight for the HDT F2b litters was significantly decreased on days 4, 7, and 14. Analysis of organ weights for the F1b parental animals showed females in the 200 ppm group with an increased brain weight. Liver weight was decreased in the 50 ppm group and increased in the 200 and 800 ppm group. The LEL for reproductive toxicity is 800 ppm (40 mg/kg/day) based on depressed pup weight. The NOEL for reproductive toxicity is 200 ppm (10 mg/kg/day); core grade minimum (Uniroyal Chemical Co., 1982)

4) Developmental toxicity - rat: Dietary levels tested: 0, 80, 160, 400, and 800 mg/kg/day; Groups of 25 to 29 impregnated Sprague-Dawley rats were orally administered dimethipin during days 6 to 15 of gestation. Because of the high mortality rate at 400 and 800 mg/kg/day after 8 days of dosing, the 30 and 160 mg/kg/day groups were added. The mean body weight gain of dams in the 160 mg/kg/day group was not significantly different during the treatment period in comparison to the controls. There were no treatment-related differences among the control and test groups with respect to implantations, live or dead fetuses, or resorptions per dam. There were no treatment-related findings among control and test groups with respect to skeletal or visceral anomalies or variations. In this study dimethipin was not teratogenic or fetotoxic at dose up to 160 mg/kg/day. Although no maternal toxicity was observed at 160 mg/kg/day,

maternal toxicity (high mortality rate) was evident at 400 and 800 mg/kg/day.; core grade minimum (Uniroyal Chemical Co., 1977a)

5) Developmental toxicity - rabbit: Dietary levels tested: 0, 7.5, 20, and 40 mg/kg/day; Four groups of 16 impregnated Dutch Belted rabbits received dosages of dimethipin by oral gavage during days 6 to 27 of gestation. The dams were sacrificed on day 28 of gestation. Three dams were sacrificed because of abortion; one each in the control, mid-, and high-dose group. The 40 mg/kg/day group females had decreased body weight during the treatment in comparison to controls. No significant differences between control and treated groups were present with respect to corpora lutea, implantations, resorptions, fetal sex distribution, and fetal weight. In this study dimethipin was not teratogenic or fetotoxic at any dose tested. The LEL for maternal toxicity is 40 mg/kg/day based on decreased body weight gain. The NOEL for maternal toxicity is 20 mg/kg/day; core grade minimum (Uniroyal Chemical Co., 1981c)

#### Other Data Reviewed

1) 18-Month Feeding (carcinogenic) - mouse: Dietary levels tested: 0, 80, 400, and 2000 ppm (0, 6, 60, and 300 mg/kg/day); Groups of 50 male and 50 female CD-1 mice were administered dimethipin in the diet for 18 months. Decreases in body weight were noted at week 13 in mid- and high-dose males and at week 61 in high-dose females. Increases in RBC were significant only in low-dose females at 78 weeks. However, higher values in comparison to controls were also noted for all male groups and in mid- and high-dose female groups at week 78. Hematocrit and hemoglobin were increased for mid- and high-dose group females at week 52 and 78; core grade minimum (Uniroyal Chemical Co., 1981d)

2) 28-Day Feeding - mouse: Dietary levels tested: 0, 250, 500, 1000, and 2000 ppm (0, 37.5, 75, 150, and 300 mg/kg/day); Groups of 10 male and 10 female albino mice were administered dimethipin in the diet for four weeks. There were no compound-related effect in mortality, toxic signs, body weight, food consumption, and gross pathology. The mean absolute and relative liver weights of males at 2000 ppm and females at 500 and 2000 ppm were statistically significant higher than controls. The LEL for systemic toxicity is 500 ppm (75 mg/kg/day) based on a statistically significant increase in mean absolute and relative liver weight in females. The NOEL for systemic toxicity is 250 ppm (37.5 mg/kg/day); core grade supplementary (Uniroyal Chemical Co., 1977b)

Data Gap(s): None

### **I.A.5. Confidence in the Oral RfD**

Study — Medium

Database — High

RfD — High

The critical study is of adequate quality and is given a medium confidence rating. Additional studies are supportive and of adequate quality and therefore the database is given a high to medium confidence rating. High to medium confidence in the RfD follows.

### **I.A.6. EPA Documentation and Review of the Oral RfD**

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — Pesticide Registration files

Agency Work Group Review — 04/08/1986, 02/21/1990

Verification Date — 04/08/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Dimethipin conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or (202)566-1676.

### **I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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### **I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Dimethipin

CASRN — 55290-64-7

Primary Synonym — Harvade

Not available at this time.

## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Dimethipin

CASRN — 55290-64-7

Primary Synonym — Harvade

Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

### **II.A. Evidence for Human Carcinogenicity**

#### **II.A.1. Weight-of-Evidence Characterization**

Classification — C; possible human carcinogen.

Basis — Classification is based on an elevated combined incidence of pulmonary adenomas/carcinomas in male, but not in female, CD-1 mice. A rat study is undergoing further evaluation.

#### **II.A.2. Human Carcinogenicity Data**

None.

#### **II.A.3. Animal Carcinogenicity Data**

Limited. Hazleton Laboratories (HL) fed Harvade in the diets of CD-1 mice (50/sex/dose group) at concentrations of 0, 80, 400 and 2000 ppm for 18 months. HL pathologists reported that there

were significant ( $p < 0.05$ ) increases in pulmonary carcinomas in the male mice fed 2000 ppm when compared with controls. When the adenomas and carcinomas of the lung were combined, there was also a significant positive trend. Likewise, when the lesions were reevaluated by Environmental Pathology Laboratories (EPL), the data on the incidence of pulmonary carcinomas indicated a significant positive dose-related trend. The combined lung adenomas and carcinomas showed a significantly higher incidence in the high-dose group when compared with controls. There was also a positive dose-related trend. The highest dose level of Harvade fed to mice in this study did not reach a maximum tolerated dose (MTD) level.

In another study, HL (1981) fed Harvade in the diets of Sprague-Dawley rats (50/sex/group) at concentrations of 0, 40, 200 and 1000 ppm for 2 years. The pathological examination of liver tumors by HL and EPL provided divergent results. HL pathologists found no effect at any dose. EPL pathologists indicated there was a significant ( $p < 0.05$ ) increase in neoplastic nodules in the 1000 ppm male rats and a significant positive dose-related trend in neoplastic nodules and in neoplastic nodules combined with carcinomas in the male rats. The HL historical control data provided by the laboratory were not useful for evaluation of the concurrent controls because of differences in protocol (e.g., route of administration, housing conditions, source of animals) across the several studies. The Office of Pesticide Programs (OPP) peer review committee (U.S. EPA, 1986) recommended that HL and EPL reevaluate the liver tumor data to reach a consensus, after which the committee would consider reevaluation. Initial pathology diagnosis of astrocytoma of the brain was revised by extensive recut and reevaluation, which showed no such diagnosis in an analysis which included all male animals at all levels except the high dose, in which 49 rats were evaluated.

#### **II.A.4. Supporting Data for Carcinogenicity**

Harvade was weakly positive in a mouse lymphoma (L5178Y) assay in the presence of metabolic activation (U.S. EPA, 1985). It was negative in two assays for mutagenicity in *Salmonella* and in a sister chromatid exchange assay using Chinese hamster cells (U.S. EPA, 1985). Harvade has no structurally-related congeners that would contribute to the evaluation.

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#### **II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure**

Not available.



## **II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**

Not available.

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## **II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)**

### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1985, 1986

The Toxicology Branch Peer Review Committee (OPP) reviewed data on Harvade.

### **II.D.2. EPA Review (Carcinogenicity Assessment)**

Agency Work Group Review — 11/10/1987

Verification Date — 11/10/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Dimethipin conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or (202)566-1676.

### **II.D.3. EPA Contacts (Carcinogenicity Assessment)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

## **VI. Bibliography**

Substance Name — Dimethipin

CASRN — 55290-64-7

Primary Synonym — Harvade

### **VI.A. Oral RfD References**

Uniroyal Chemical Company. 1977a. EPA Accession No. 070237. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Uniroyal Chemical Company. 1977b. MRID No. 00160460. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Uniroyal Chemical Company. 1981a. MRID No. 00085653, 00145225. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Uniroyal Chemical Company. 1981b. EPA Accession No. 070237. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Uniroyal Chemical Company. 1981c. EPA Accession No. 070237. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Uniroyal Chemical Company. 1981d. MRID No. 00079998. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Uniroyal Chemical Company. 1982. MRID No. 00094792. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

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### **VI.B. Inhalation RfC References**

None

## VI.C. Carcinogenicity Assessment References

Hazleton Laboratory. 1981. Cited in U.S. EPA, 1986.

U.S. EPA. 1985. Toxicology Branch (OPP) memorandum on Harvade. May 13.

U.S. EPA. 1986. Toxicology Branch (OPP) Peer Review Committee memorandum on Harvade. July 24.

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## VII. Revision History

Substance Name — Dimethipin

CASRN — 55290-64-7

Primary Synonym — Harvade

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
03/01/1990	I.A.	NOTE added; assessment reevaluated - no RfD change
05/01/1990	I.A.	Reevaluated Oral RfD on-line - no RfD change
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

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## VIII. Synonyms

Substance Name — Dimethipin

CASRN — 55290-64-7

Primary Synonym — Harvade

Last Revised — 01/31/1987

- 55290-64-7
- Dimethipin
- p-DITHIANE, 2,3-DEHYDRO-2,3-DIMETHYL-, TETROXIDE
- Harvade
- UBI-N252