

1,4-Dithiane; CASRN 505-29-3

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 1,4-Dithiane

File First On-Line 03/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/01/1993*
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	03/01/1991*

*A comprehensive review of toxicological studies was completed (05/27/05) - please see sections I.A.6. and II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 1,4-Dithiane

CASRN — 505-29-3

Last Revised — 03/01/1993

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
Nasal olfactory lesions	NOAEL: None LOAEL: 105 mg/kg-day	10,000	1	1E-2 mg/kg-day
90-Day Gavage Rat Study				
Schieferstein et al., 1988				

*Conversion Factors: None

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

Schieferstein, G.J., W.G. Sheldon, S.A. Cantrell and G. Reddy. 1988. Subchronic toxicity study of 1,4-dithiane in the rat. *Fund. Appl. Toxicol.* 11: 703-714.

Schieferstein et al. (1988) (commissioned by the US Army [Schieferstein, 1987]) gavaged groups of CD rats (30/sex/dose) for 90 days with 1,4-dithiane suspended in sesame seed oil at 0, 105, 210, or 420 mg/kg-day. The animals were observed twice daily for signs of toxicity. At terminal sacrifice, all surviving animals were necropsied and organs were weighed. All high-dose and control animals received histopathological examinations. Organs that showed treatment related lesions in the high-dose group were examined at successively lower doses until a no-effect dose was found or until all animals were examined. Clinical chemistry and hematological parameters were examined on six animals per sex in each group on days 30, 60, and 90. Six animals died from gavage accidents and the cause of death of a seventh animal was not identified.

No overt toxicity, treatment-related mortality, or ophthalmologic changes were reported in any of the animals. No significant treatment related changes occurred in body weight and in food and water consumption. Females at all dose levels had absolute brain weights that were significantly ($p < 0.02$) lighter than that of the control animals. In the 420 mg/kg-day female group, relative liver weight was significantly ($p < 0.02$) higher than that of controls and was associated with mild histopathology characterized by hypertrophy of the centrilobular hepatocytes (26/30), and cytoplasmic vacuolation of hepatocytes in the periportal region of the lobules (6/30). Males (26/28) in the 420 mg/kg-day group had eosinophilic cytoplasmic granules in renal convoluted tubules which were more severe in the distal tubules. Males given 210 mg/kg-day had significant ($p < 0.02$) increases in absolute kidney and spleen weights. In the 105 mg/kg-day dose group, females had significantly ($p < 0.02$) lower brain and higher spleen and thymus weights; males had significantly ($p < 0.02$) higher absolute spleen and kidney weights. With the exception of increased liver weights in the high-dose females, when organ-to-terminal body weight ratios were evaluated, there was no statistically significant effects. The lower brain weight in treated females was only 1 to 3% lighter than that of control animals, possibly attributable to necropsy technique, and is not considered to be biologically significant.

Even though females in the 105 mg/kg-day group had significant amylase decreases, the biological significance is unclear; there were no pathological abnormalities in the pancreases or salivary glands. There were no treatment related differences between dosed animals and controls with respect to other clinical chemistry and hematological parameters.

Nasal lesions, characterized by deposition of chemically undefined crystals, were found in both sexes of all treatment groups. Crystals were observed in 2/30 males at the 105 mg/kg-day dose and in all males (28/28) at both the 210 mg/kg-day and 420 mg/kg-day doses. In females the crystals were observed in 24/29 at the 105 mg/kg-day dose and in all (30/30) at both the 210 mg/kg-day and 420 mg/kg-day dose levels. The crystals were associated with granulomatous inflammation of the mucosa characterized by phagocytosis. Crystals that were closely associated with bone and cartilage induced, in some cases, focal osseous and cartilaginous inflammation and degeneration. The crystals were detected in the renal pelvis of one animal. Although, the investigators were not able to determine the composition of the crystals, the appearance of these crystals in the nasal epithelium are clearly treatment- and dose-related.

The LOAEL for this study is 105 mg/kg-day based upon the occurrence of nasal lesions in female rats. A NOAEL could not be determined because effects were observed at the lowest dose tested.

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

UF — This uncertainty factor includes factors of 10 each for interspecies extrapolation and intraspecies extrapolation for use of a LOAEL. An additional factor of 10 is applied for the use of a subchronic study and the lack of reproductive toxicity, developmental toxicity and chronic toxicity studies. Sometimes a factor of 3000 is applied when there are four areas of uncertainty to account for overlapping uncertainty between areas of deficiencies. In this case, a full factor of 10,000 was applied because of greater uncertainty introduced by database deficiencies (e.g., only one subchronic toxicity study in one species, lack of toxicokinetic data) and the nebulous biological significance of the nasal lesions.

MF — None

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

No quantitative data on the absorption, distribution, metabolism, or excretion of 1,4-dithiane in humans or experimental animals were found in the available literature. However, because of systemic effects observed in rats orally dosed with 1,4-dithiane, it can be assumed that there is absorption from the gastrointestinal tract.

The significance of the nasal lesions that developed in rats exposed to 1,4-dithiane by an oral route is not clear. The investigators did not analyze the crystals that were associated with the lesions to determine if they were related chemically to 1,4-dithiane. They did hypothesize that the animals may have inhaled the chemical; however, none of the control animals, which were housed and dosed in the same atmosphere as the treated animals, developed nasal lesions or crystals.

No studies on the health effects of 1,4-dithiane in humans were found in the literature.

I.A.5. Confidence in the Oral RfD

Study — Low

Database — Low

RfD — Low

The 90-day study in rats was well designed. It had an adequate number of animals of both sexes and evaluated a variety of gross, histological, hematological, and clinical endpoints. There is more confidence in selecting a critical effect when numerous endpoints are monitored because it decreases the possibility that a possible effect was not observed. Furthermore, a NOAEL was not determined and the significance of the appearance of the nasal lesions has not been determined.

Confidence in the database is low because the 90- day study by Schieferstein et al. (1988) is the only existing study, with only one species having been tested, and there is no reproductive, developmental, or chronic toxicity studies available. The low rating for the study and the low rating for the database result in a low level of confidence in the RfD.

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

Source Document — U.S. EPA, 1992

Other EPA Documentation — None

Agency Work Group Review — 06/24/1992

Verification Date — 06/24/1992

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for 1,4-Dithiane and a change in the RfD is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at 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 (internet address).

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

Substance Name — 1,4-Dithiane

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Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,4-Dithiane

CASRN — 505-29-3

Last Revised — 03/01/1991

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 — D; not classifiable as to human carcinogenicity

Basis — Based on no data in humans and animals.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

None.

II.A.4. Supporting Data for Carcinogenicity

1,4-Dithiane was not mutagenic, either with or without metabolic activation, in the Ames Salmonella/mammalian microsome mutagenicity assay (Sano and Korte, 1985). *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to 1,4-dithiane over a range of concentrations (5, 1, 0.2, 0.04, 0.008, and 0.016 mg/plate) in the presence and absence of exogenous S9 metabolic activation. The dose levels represent concentrations that decrease from the minimum toxic level (the maximum or limit dose) by dilution factors of five. The

responsiveness of the tester strains was confirmed using four known mutagens as positive controls.

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

None.

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

None.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1990

The Health Advisory for 1,4-Dithiane has received Agency and external review.

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

Agency Work Group Review — 01/10/1991

Verification Date — 01/10/1991

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for 1,4-Dithiane and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at 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 (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — 1,4-Dithiane

CASRN — 505-29-3

VI.A. Oral RfD References

Schieferstein, G.J. 1987. Subchronic toxicity study on 1,4-dithiane. U.S. Army Medical Bioengineering Research and Development Laboratory, Ft. Detrick, MD. Available from NTIS, Springfield, VA. No. ADA184771.

Schieferstein, G.J., W.G. Sheldon, S.A. Cantrell and G. Reddy. 1988. Subchronic toxicity study of 1,4-dithiane in the rat. *Fund. Appl. Toxicol.* 11: 703-714.

U.S. EPA. 1992. Health Advisory for 1,4-Dithiane. Office of Water, Office of Science and Technology, Washington, DC. Available from NTIS, Springfield, VA. PB93-117026.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Sano, S.K. and D.W. Korte. 1985. Mutagenic potential of p-dithiane. Toxicology Series 95. Letterman Army Institute of Research, San Francisco, CA, to U.S. Army Medical Research and Development Laboratory, Fort Detrick, Frederick, MD. Institute Report No. 207.

U.S. EPA. 1990. Drinking Water Health Advisory for 1,4-Dithiane. Office of Drinking Water, Washington, DC. (Draft)

VII. Revision History

Substance Name — 1,4-Dithiane
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Date	Section	Description
03/01/1991	II.	Carcinogenicity assessment on-line
03/01/1993	I.A.	Oral RfD summary on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
06/22/2005	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — 1,4-Dithiane
CASRN — 505-29-3
Last Revised — 03/01/1991

- 505-29-3
- 1,4-Dithiane
- NSC 24178
- p-Dithiane
- 1,4-DITHIACYCLOHEXANE
- 1,4-Dithiin, tetrahydro-