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Acetone; CASRN 67-64-1; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Acetone

File First On-Line 03/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	00/00/0000
Inhalation RfC Assessment (I.B.)	no data	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Acetone

CASRN -- 67-64-1

Last Revised -- 00/00/00

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.

This value replaces a previous RfD of 0.1 mg/kg-day that was entered on August 1, 1993. The change in the value is attributed to a newer study (NTP, 1991; Dietz et al., 1991) that is more

comprehensive and employs a mode of exposure that more realistically mimics what humans can expect. The previous study (Sonawane et al., 1988) used a gavage application for ingestion whereas the current study uses drinking water ingestion. A second factor is that the previous study applies uncertainty factors totaling 1,000 whereas the current study employs uncertainty factors of 3,000 (discussion of the uncertainty factors is discussed below). Additionally, the data reported in the gavage study are extracted from an abstract reported at a national meeting. The current study has the benefit of undergoing both NTP and publication-level peer review.

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Nephropathy and anemia	NOAEL: 900 mg/kg/day LOAEL: 1,700 mg/kg/day BMDL: (not determined)	3,000	1	0.3 mg/kg/day
Dietz et al., 1991 NTP, 1991				

*Conversion Factors and Assumptions -- actual dose tested (time-weighted average).

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Dietz, DD; Leininger, JR; Rauckman, EJ. (1991) Toxicity studies of acetone administered in the drinking water of rodents. *Fundam Appl Toxicol* 14:347-360.

National Toxicology Program (NTP). (1991) Toxicity studies of acetone (CAS No. 67-64-1) in F344/N rats and B6C3F₁ mice (drinking water studies). NTP, Research Triangle Park, NC. NTP TOX 3, NIH Publication No. 91-3122.

Groups of 10 male and 10 female F344/N rats were administered acetone in the drinking water at concentrations of 0, 2,500, 5,000, 10,000, 20,000, or 50,000 ppm for 13 weeks (NTP, 1991; Dietz et al., 1991). Time-weighted average doses for males were 0, 200, 400, 900, 1,700, and 3,400 mg/kg/day, respectively, and for females were 0, 300, 600, 1,200, 1,600, and 3,100 mg/kg/day, respectively. No deaths occurred in any group. Water consumption was decreased in high-dose males and in females given 20,000 and 50,000 ppm. Mean final body weight of the high-dose males was 81% of the controls; body weights of the females were unaffected by treatment. No clinical signs of toxicity or ophthalmic abnormalities were observed in any group. At necropsy, significant ($p \neq 0.05$ or 0.01) increases in the following organ weights were noted: relative kidney weights were 114% of controls for 20,000-ppm females and 126% and 123% of controls for 50,000-ppm males and females, respectively; relative liver weights were 110% and 112% of controls for 20,000-ppm males and females, respectively, and 115% and 105% of controls for 50,000-ppm males and females,

respectively; and relative testis weights were 119% of controls at 50,000 ppm. Liver weight changes were not associated with microscopic lesions and were thought to be a result of enzyme induction. In high-dose males, depressed sperm motility, caudal weight, and epididymal weight and an increased incidence of abnormal sperm were seen (data for testicular lesions were given only for the 0, 2,500, 10,000, and 50,000 ppm groups; see also Section 4.3.1.1). Males given the two highest concentrations of acetone had increases in both the incidence and severity of nephropathy, indicating early onset and enhanced progression of the disease. In males given 0, 2,500, 5,000, 10,000, 20,000, or 50,000 ppm, nephropathy was observed in 6/10, 8/10, 8/10, 9/10, 10/10, and 10/10, respectively, with severity ratings of 1.2, 1.0, 1.0, 1.0, 1.9, and 1.9, respectively (1 = minimum, 2 = mild, 3 = moderate, 4 = severe). Nephropathy was not observed in females. Pigment deposition in the spleen was observed in 10/10 males in the 20,000- and 50,000-ppm groups compared with 0/10 controls.

Also at 20,000 and 50,000 ppm of acetone, males had significant ($p \neq 0.05$ or 0.01) changes in hematology. For the 20,000- and 50,000-ppm groups, leukocytes were 125% and 133% of controls, erythrocyte counts were 92% and 90% of controls, reticulocyte counts were 75% and 68% of controls, hemoglobin levels were 97% of controls in both groups, mean corpuscular hemoglobin was 102% and 108% of controls, and mean cell volume was 105% and 109% of controls. These changes in red cell parameters of 20,000- and 50,000-ppm males were consistent with mild macrocytic normochromic anemia with a depressed regenerative response. A mild leukocytosis was also observed in high-dose females, but this single difference was not considered biologically significant. Clinical chemistry parameters were not measured.

On the basis of these findings, the NOAEL is 900 mg/kg/day and the LOAEL is 1,700 mg/kg/day based on early onset and enhanced progression of nephropathy and macrocytic normochromic anemia with a depressed regenerative response in males (NTP, 1991; Dietz et al., 1991).

The previous assessment based the determination of the RfD on a 90-day gavage study of male and female rats (Sonawane et al., 1991). The RfD for the previous study was 0.1 mg/kg/day. Although the NTP study provides a higher RfD than the American Biogenics study, the NTP study was selected for several reasons. First, the NTP study is a drinking water study. In comparison with a gavage study, a drinking water study more realistically mimics an exposure scenario that one would expect from contaminated groundwater. Furthermore, the drinking water study has been published in a peer-reviewed journal. The gavage study is unpublished and reported in an abstract (Sonawane et al., 1991).

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = Uncertainty factors (UFs) of 10 each were applied for intraspecies extrapolation, for extrapolating from a subchronic to a chronic exposure, and for database insufficiency, and a partial UF of 3 ($10^{1/2}$) was used for interspecies extrapolation.

The intraspecific extrapolation was applied to account for differences between effects on healthy individuals and more sensitive members of the population. This is consistent with the prior assessment.

The subchronic-to-chronic extrapolation was applied to compensate for the length of the principal study. Acetone demonstrates rapid absorption into the body followed by rapid metabolism and excretion. However, repeated insult over an extended period of time could lead to more pronounced effects. A 10-fold UF was applied in the previous assessment.

The full UF for database insufficiency was applied to compensate for the absence of a complete dataset for reproductive and developmental effects, and for a chronic study. The previous assessment did not include a UF for database insufficiency.

A partial UF of 3 ($10^{1/2}$) was used for interspecies extrapolation because the lesions were transient (liver), of questionable biological significance to humans (kidney), not severe enough to adversely affect the health of the animals clinically (kidney, hematopoietic, testicular), and/or not supported by histopathology (testicular) or clinical chemistry abnormalities (kidney). The previous assessment applied a full UF of 10 for the interspecies extrapolation.

A UF for a LOAEL-to-NOAEL extrapolation is unnecessary. The RfD was based on a NOAEL. The UF was not applied in the previous assessment.

Modifying factors were not applied because the study was well conducted, used a relevant exposure method (drinking water), and evaluated numerous parameters.

1.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

American Biogenics Corporation. (1986) Ninety day gavage study in albino rats using acetone. American Biogenics Corporation, Decatur, IL. (Unpublished)

Sonawane, B; de Rosa, C; Rubenstein, R. (1986) Estimation of reference dose (RfD) for oral exposure of acetone. 7th Annual Meeting, American College of Toxicology, November 16-19, 1986. p. 21 (abstr.)

Groups of 30 male and female Sprague-Dawley rats were administered acetone by oral gavage at doses of 0, 100, 500, or 2,500 mg/kg/day for 90 days; 10 animals/sex/group were designated for interim sacrifice at 46-47 days (American Biogenics Corp., 1986; Sonawane et al., 1986). Survival, body weights, food consumption, ophthalmology examinations, and gross necropsy findings were similar between the treated and control groups. Clear salivation was observed between day 27 and study termination in a total of 21 males and 24 females at the highdose. Red cell parameters (hemoglobin, hematocrit, mean cell volume, and/or mean cell hemoglobin) in the high-dose groups were significantly ($p \# 0.05$ or 0.01) increased for males at interim sacrifice and for males and females at final sacrifice; however, the magnitude of the increases was not biologically significant. Differences in clinical

chemistry parameters were not dose-related and were not consistent over time or between sexes. Absolute and/or relative liver and kidney weights were significantly ($p \leq 0.05$ or 0.01) increased in the mid-dose females and in the high-dose males and females as compared with their respective controls. Relative (to brain and/or body weights) liver and kidney weights of the high-dose males were 111%-117% of the controls. Absolute kidney weights of mid-dose females were 110%-112% of controls and absolute and relative kidney weights of the high-dose females were 114%-118% and 111%-123%, respectively, of control levels. Absolute and relative liver weights of mid-dose females were 115% and 113%, respectively, and of high-dose females were 121% and 115%-125%, respectively, of the controls. Although incidence rates were similar between the treated and control groups, a marked increase in severity of tubular degeneration of the kidneys in mid- and high-dose males and females and hyaline droplet accumulation in mid- and high-dose males was observed. Based on organ weight changes and kidney lesions in males and females, the LOAEL for this study is 500 mg/kg/day and the NOAEL is 100 mg/kg/day (Sonawane et al., 1986).

This study supports the kidney and hematopoietic system as target organs for acetone in the rat. Although an RfD derived from this gavage study is more conservative, the selected study using the drinking water route more closely mimics potential long-term human exposure scenarios.

Limited human studies have shown that clinical signs and symptoms in factory workers exposed to acetone vapors were transient, intermittent, and associated with short-term exposure to peak concentrations.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium

Database -- Low

RfD -- Medium

Confidence in the principal study is medium because both males and females were used and an extensive number of parameters were measured; however, the confidence is not high because the study is a subchronic rather than a chronic study. The database is rated low because a limited number of studies are available, including one supporting study, and the database does not include a chronic, developmental, or reproductive study. The overall confidence in this RfD assessment is medium largely because, although the principal study was well-conducted and applied a method of administration that is relevant to human exposure this value is based on a subchronic study.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA, 2001.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to the Toxicological Review of Acetone (U.S. EPA, 2001).

Other EPA Documentation -- None.

Agency Consensus Date -- 00/00/00

__I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (fax), or RIH.IRIS@EPAMAIL.EPA.GOV (Internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Acetone

CASRN -- 67-64-1

Last Revised -- 00/00/00

The Inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m^3 . In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are 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.B.1. INHALATION RfC SUMMARY

No RfC is recommended at this time. The previous IRIS assessment on acetone did not derive an RfC.

__I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Not available.

__I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

Not applicable.

___ I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

Not applicable.

___ I.B.5. CONFIDENCE IN THE INHALATION RfC

Not applicable.

___ I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Not applicable.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Acetone

CASRN -- 67-64-1

Last Revised -- 00/00/0000

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 $\mu\text{g/L}$ drinking water or risk per $\mu\text{g}/\text{cu.m}$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with 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.

The current weight of evidence remains the same as previous determinations. There have been no significant contributions in the form of studies that can be used to better assess the potential for cancer from exposure to acetone. This assessment contains a weight-of-evidence determination based on the proposed Cancer Assessment Guidelines (U.S. EPA, 1996).

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the current Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1987a) the weight of evidence for carcinogenicity from animal and human studies is classified as Group D *-not classifiable as to human carcinogenicity*.

Under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), acetone's potential for human carcinogenicity may best be described as "*cannot be determined*" based on inadequate data to perform an assessment.

Under EPA's Risk Assessment Guidelines of 1986 (U.S. EPA, 1987a), acetone is classified into cancer weight of evidence. Much of the acetone that is absorbed into the body is readily metabolized via three gluconeogenic pathways to glucose. The physicochemical properties of acetone do not lend themselves to reactivity with biologically active molecules that would be expected to support the onset of cancer. Genotoxicity studies are almost uniformly negative, human exposure from industrial applications has failed to demonstrate a carcinogenic potential (Ott et al., 1983a,b), and the chemical has been used as a solvent/vehicle for dermal studies in animals (NTP, 1991, 1995, 1997). To date there have been no animal toxicity studies that have demonstrated carcinogenic potential for low molecular weight, saturated ketones (U.S. EPA, 2001).

The previous assessment gave acetone a weight of evidence classification of D, *not classifiable as to human carcinogenicity*. The basis was a lack of data concerning carcinogenicity in humans or animals. The IRIS Summary cited no human or animal data and only cited many of the same genotoxicity studies that are cited in this assessment (U.S. EPA, 1987b).

___II.A.2. HUMAN CARCINOGENICITY DATA

No significant risk of death from malignant neoplasm, or any other cause, was found in workers at a cellulose acetate plant where acetone was used as a solvent when compared with the general population. Employment ranged from 3 months to 23 years with time-weighted-average acetone concentrations of 380-1,070 ppm depending on job category (Ott et al., 1983a,b; as reviewed in ATSDR, 1994). In this study, the 948 acetone-exposed workers were the reference cohort for comparison with workers exposed to acetone plus methylene chloride; comparisons to unexposed controls were not made. For the acetone-exposed workers, the total number of deaths observed from all causes was 24 and 3 for men and women, respectively, compared with the total expected of 53.8 and 6.7 for men and women, respectively. Shortcomings of this study include the fact that the acetone-exposed group served as a reference cohort and not the exposed cohort, and that cancer was a secondary consideration and was not evaluated in depth.

II.A.3. ANIMAL CARCINOGENICITY DATA

There are no chronic studies on acetone that can be used to evaluate the carcinogenicity of acetone in animals. Acetone has been extensively used as a vehicle in dermal studies in mice (NTP, 1991; 1995; 1997; Ward et al., 1986; Zakova et al., 1985). Generally mice receive one to two applications per week for up to 2 years. These studies lack a naive control with which to compare the vehicle controls.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

No significant risk of death from malignant neoplasm, or any other cause, was found in workers at a cellulose acetate plant where acetone was used as a solvent when compared with the general population. Employment ranged from 3 months to 23 years with time-weighted-average acetone concentrations of 380-1,070 ppm depending on job category (Ott et al., 1983a,b; as reviewed in ATSDR, 1994)

The genotoxicity of acetone has been well studied and reviewed, with the results almost entirely negative (ATSDR, 1994; U.S. EPA, 1988, 1998; WHO, 1998). All studies evaluated by the GENETOX panel and cited in the GENETOX database were negative, with the exception of one study for which no conclusion was drawn (GENETOX, 1999). Examples of a few of the studies are presented in the following discussion. Neither sister chromatid exchange nor chromosome aberrations were induced in Chinese hamster ovary cells by acetone at a concentration not exceeding 1% in the culture flask with or without metabolic activation (Loveday et al., 1990). Concentrations of acetone up to 0.6% did not change the background DNA synthesis rate, i.e., induce unscheduled DNA synthesis, in cultured human epithelial cells; higher concentrations up to 10% actually inhibited background synthesis in a concentration-related manner (Lake et al., 1978). The chemical was negative at concentrations up to 10 mg/plate in the Ames reversion test with five strains of *S. typhimurium* in the presence or absence of a metabolic activation system (NTP, 1991; De Flora et al., 1984).

In contrast to the above reports, acetone, at concentrations of 6.98%-7.83%, produced aneuploidy in an inconsistent manner, but did not induce recombination or point mutation in *Saccharomyces cerevisiae*. However, overnight storage on ice of cells in growth medium containing acetone resulted in strong induction of aneuploidy (Zimmermann et al., 1985). The significance of this study is unknown.

To date there have been no positive carcinogenicity studies for low-molecular-weight saturated ketones by either the inhalation or oral routes. Acetone is commonly used as a vehicle for chronic dermal studies (U.S. EPA, 2001).

__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, 2001.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to the Toxicological Review of Acetone (U.S. EPA, 2001).

__II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- 00/00/0000

__II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (fax), or RIH.IRIS@EPAMAIL.EPA.GOV (Internet address).

_III. [reserved]

_IV. [reserved]

_V. [reserved]

_VI. BIBLIOGRAPHY

Acetone

CASRN -- 67-64-1

Last Revised -- 00/00/0000

__VI.A. ORAL RfD REFERENCES

American Biogenics Corporation. (1986) Ninety day gavage study in albino rats using acetone. American Biogenics Corporation, Decatur, IL. (unpublished).

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__VI.B. INHALATION RfC REFERENCES

Not applicable.

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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NTP. (1997) Toxicology and carcinogenesis studies of 1,2-dihydro-2,2,4-trimethylquinoline (CAS No. 147-47-7) in F344/N rats and B6C3F₁ mice (dermal studies) and the dermal initiation/promotion study in female Sencar mice. NTP, Research Triangle Park, NC NTIS Publication # PB98-101009.

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VII. REVISION HISTORY

Acetone

CASRN -- 67-64-1

<u>Date</u>	<u>Section</u>	<u>Description</u>
03/01/1988	I.A.5.	Confidence levels revised
07/01/1989	VI.	Bibliography on-line
01/01/1990	II.	Carcinogen assessment under review
07/01/1990	II.	Carcinogen assessment on-line
07/01/1990	IV.F.1.	EPA contact changed
07/01/1990	VI.C.	Carcinogen references added
12/01/1990	I.A.2.	Text edited
12/01/1990	I.A.7.	EPA contact changed
12/01/1990	II.A.4	Text edited
01/01/1992	IV.	Regulatory actions updated
08/01/1993	I.A.	Oral RfD noted as pending change
08/01/1993	I.A.6	Work group review date added
00/00/0000	I.A.	Oral RfD updated
00/00/0000	I.B.	Inhalation RfC updated
00/00/0000	II.	Cancer assessment updated

_VIII. SYNONYMS

Acetone

CASRN -- 67-64-1

Last Revised -- 00/00/00

ACETONE

Acetone

DIMETHYLFORMALDEHYDE

DIMETHYLKETAL

DIMETHYL KETONE

KETONE, DIMETHYL

KETONE PROPANE

beta-KETOPROPANE

METHYL KETONE

PROPANONE

2-PROPANONE

PYROACETIC ACID

PYROACETIC ETHER

RCRA WASTE NUMBER U002

UN 1090