

Acetone; CASRN 67-64-1

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 Acetone

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/31/2003
Inhalation RfC (I.B.)	qualitative discussion	07/31/2003
Carcinogenicity Assessment (II.)	yes	07/31/2003

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 — 07/31/2003

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.

The RfD generated in this assessment differs from the previous RfD (0.1 mg/kg-day). This difference is accounted for, in part, by a change in the principal study. The previous RfD is based on the gavage study conducted by American Biogenics Corp. (1986). The administered doses were 0, 100, 500, or 2,500 mg/kg-day. The critical effect noted was kidney pathology, and the NOAEL was 100 mg/kg-day. The RfD invoked uncertainty values of 10 for intraspecies and interspecies extrapolation, and 10 for extrapolation from a subchronic to a chronic exposure scenario. Although the point of departure noted in the gavage study is lower, the study used as the principal study in this assessment utilizes the drinking water route which more closely mimics potential long-term human exposure scenarios and is considered more thorough.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Nephropathy	NOAEL: 900 mg/kg-day	1000	1	0.9 mg/kg-day
Subchronic drinking water study in rats	LOAEL: 1700 mg/kg-day			
(Dietz, et al., 1991; NTP, 1991)	BMDL: not determined			

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

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

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 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 acetone. 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, statistically significant ($p \leq 0.01$ or 0.05) 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 result from enzyme induction. In high-dose males, depressed sperm motility, caudal weight, epididymal weight and an increased incidence of abnormal sperm were seen (data for testicular effects were given only for the 0, 2,500, 10,000, and 50,000 ppm groups; see also Section 4.3.1.1 of the Toxicological Review). Males given the two highest concentrations of acetone had increases in 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 acetone, nephropathy was observed in all treatment groups including the controls. As such, the incidence of nephropathy rated as mild was taken as the indicator of toxicity. For the 0, 2,500, 5,000, 10,000, 20,000, and 50,000 ppm doses the incidence of minimal nephropathy was 5, 8, 8, 9, 1, and 1 (out of 10 animals) and for mild nephropathy 1, 0, 0, 0, 9 and 9 (out of 10 animals), respectively. The authors of the study identify the kidney effects as the most prominent chemically-related effect. 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.

Other endpoints were noted at 20,000 and 50,000 ppm doses of acetone, including statistically significant ($p \leq 0.01$ or 0.05) changes in hematology in males. For the 20,000 and 50,000 ppm groups, leukocytes were 125 and 133% of controls, erythrocyte counts 92% and 90% of controls, reticulocyte counts 75 and 68% of controls, hemoglobin levels 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, respectively. Changes in red blood cell parameters of 20,000 and 50,000 ppm males were consistent with mild macrocytic normochromic anemia with a depressed regenerative response. Mild leukocytosis was also observed in high-dose females, but this single difference was not considered biologically significant. Clinical chemistry parameters were not measured. In summary, the testis, kidney, and hematologic system were identified by the study authors as target organs for male rats, with a LOAEL of 1,700 mg/kg-day and a NOAEL of 900 mg/kg-day. A LOAEL for female rats was not identified.

Groups of 10 male and 10 female B6C3F1 mice were administered acetone in the drinking water at concentrations of 0, 1,250 (males only), 2,500, 5,000, 10,000, 20,000, or 50,000 (females only) ppm for 13 weeks (NTP, 1991; Dietz et al., 1991). Time-weighted average

doses for males were 0, 380, 600, 1,400, 2,300, and 4,900 mg/kg-day, respectively, and for females 0, 900, 2,000, 4,200, 5,900, and 11,000 mg/kg-day, respectively. No deaths occurred and no clinical signs of toxicity were observed in any group. Water consumption was not affected in males; however, dose-related decreases in water consumption were seen in all treated females. Body weight and growth of the treated animals were not affected in either sex. Hematology parameters, sperm morphology, and vaginal cytology were not affected by acetone treatment. Organ weights from the treated males were similar to the controls. However, statistically significant ($p \leq 0.01$ or 0.05) increases in high-dose female absolute and relative liver weights were 113 and 110% of controls, respectively. Statistically significant ($p \leq 0.05$) decreases in absolute and relative spleen weights were 89 and 88% of controls, respectively. The only microscopic lesion seen in mice was centrilobular hepatocellular hypertrophy, observed in two high-dose females and considered due to enzyme induction. Mild hepatic changes were observed in males exposed to $\geq 20,000$ ppm for 14 days (see Section 4.2.1.1 of the Toxicological Review) but did not persist after 13 weeks of exposure, suggesting the development of tolerance toward acetone. In summary, the liver was identified as the target organ in male and female mice. The reference to this effect as an adverse effect is uncertain because the morphological changes may reflect induction of enzymes rather than an untoward effect on the liver. Effects that were noted in the rat, particularly males, were not evident with the mice. The LOAELs for males and females were 4,900 and 11,000 mg/kg-day, respectively, and the NOAELs were 2,300 and 5,900 mg/kg-day, respectively. It should be noted that the LOAEL for male mice was selected by the study authors on the basis of the transient findings in the 14-day study.

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). 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 high dose. Red blood cell parameters (hemoglobin, hematocrit, mean cell volume, and/or mean cell hemoglobin) in the high-dose groups increased in a statistically significant ($p \leq 0.01$ or 0.05) manner for males at interim sacrifice and for males and females at final sacrifice. However, the study author did not consider the magnitude of the increases to be biologically significant. One animal in the control group, one in the low dose group, and four in the high dose group died prematurely; the deaths were attributed to dosing errors. Differences in clinical chemistry parameters were not dose-related and were not consistent over time or between sexes. Statistically significant ($p \leq 0.01$ or 0.05) increases in the absolute and/or relative liver and kidney weights were observed in the mid-dose females and in the high-dose males and females when 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 nephropathy incidence rates were similar between the treated and control groups, an increase in the 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. Statistical comparisons were not conducted for the increased severity of the kidney effect. However, the nephropathy exhibited a dose-response with respect to the numbers of animals affected. The numbers of male rats exhibiting tubular degeneration characterized as mild or moderate (in comparison with minimal) were 0, 1, 9, and 17 out of 30 animals for the 0, 100, 500, and 2,500 mg/kg-day group, respectively. 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.

There are no human studies or chronic animal studies available for the derivation of an RfD. Two shorter duration studies are available, including a short-term exposure (14 days) study using 5 animals per dose group (NTP, 1991; Dietz et al., 1991) that is not considered suitable for the derivation of an RfD due to the acute nature of the dosing regimen. The principal study identified for derivation of the oral RfD is the subchronic drinking water study (NTP, 1991; Dietz et al., 1991). Male rats appeared to be the most sensitive species, with the kidney, hematologic system, and testes identified as target organs. Enhanced progression of mild nephropathy and effects consistent with macrocytic normochromic anemia with a depressed regenerative response were found at a high-dose of 1,700 mg/kg-day. In addition, depressed sperm motility, caudal and epididymal weights, and an increased incidence of abnormal sperm occurred at 3,400 mg/kg-day. A LOAEL of 1,700 mg/kg-day and a NOAEL of 900 mg/kg-day were identified for mild nephropathy.

The American Biogenics Corp. (1986) gavage study is used as a supporting study. Organ weight changes and kidney lesions were identified at a dose of 500 mg/kg-day. While the gavage study included clinical chemistry analyses, the data failed to show dose-related effects consistent with the nephropathy noted in the histology, thereby raising questions about the significance of the effect. Differences in the observed effect level in the drinking water study versus the gavage study may relate to the method of administration. Acetone is readily absorbed through the gastrointestinal tract (see Section 3.1 of the Toxicological Review). Under conditions of short-term elevated exposure levels such as those produced in gavage or bolus experiments, more acetone appears to be shunted to the kidney, producing higher concentrations in the urine and higher rates of metabolism through the propanediol pathway compared with the more gradual administration through drinking water. This could account

for differences in the nephropathy severity levels observed with drinking water compared with gavage administration. For this reason, the gavage study was not chosen as the principal study.

Mild nephropathy was chosen as the critical effect, and was seen in male rats only in the Dietz et al. (1991) and NTP (1991) study. The choice of critical effect is supported by the report of tubular degeneration of the kidneys in male and female rats and hyaline droplet accumulation in males at 500 and 2,500 mg/kg-day in the American Biogenics Corp. (1986) study. An oral gavage study on isopropanol (Bevan et al., 1995), which is metabolized primarily to acetone, also supports nephropathy as the critical effect. In this two-generation reproductive toxicity study, kidney effects (including an increased number of hyaline droplets in epithelial cells of the proximal tubules and an increase in severity of epithelial degeneration) were noted at 500 and 1000 mg/kg-day P1 male rats and also at 100 mg/kg-day in P2 male rats. Changes in hematological parameters (erythrocyte and leukocyte counts and hemoglobin levels) in male rats, but not mice, were noted in the Dietz et al. (1991) study. Red blood cell parameters only were significantly affected at 2,500 mg/kg-day in male rats in the American Biogenic Corp. (1986) study.

The data were analyzed using the NOAEL/LOAEL approach using a point of departure of 900 mg/kg-day based on an increased incidence of mild nephropathy. The available PBPK models for oral exposure (see Section 3.5 of the Toxicological Review) were not used for the derivation of the human equivalent dose because they have not been validated against human data.

Minimal or mild nephropathy was present in all groups. One out of ten animals in the control group was rated with a mild degree of nephropathy. No animals in groups dosed at intermediate levels of 10,000 ppm or lower were rated with mild nephropathy. In contrast, nine out of ten animals dosed at both 20,000 and 50,000 ppm were rated with mild nephropathy. This type of response is not amenable to benchmark dose modeling, since a graded dose-response curve is lacking (a response of 1/10 animals for controls compared with a response of 9/10 animals at the lowest response level) and the lowest response is much higher than what might be considered a low, e.g., 10%, benchmark response. For this reason, the NOAEL/LOAEL approach was used.

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

UF = 1000

The following UFs are applied to the effect level: 10 for consideration of intraspecies variation (UF_H; human variability), 3 (10^{1/2}) for extrapolation for interspecies differences (UF_A; animal to human), 3 to account for extrapolation from subchronic studies (UFs; subchronic to

chronic), and 10 to account for a deficient database (UFD). The total UF = $10 \times 10^{1/2} \times 10^{1/2} \times 10 = 1000$.

An UF of 10 was applied for intraspecies uncertainty to account for susceptible subpopulations. This factor accounts for humans who may be more susceptible to acetone exposure than the general population but for whom data are not available. This may include individuals who have elevated levels of endogenous acetone due to high-fat low-carbohydrate diets, fasting conditions, or uncontrolled diabetes. In addition, the production of glycated endproducts may be increased due to acetone exposure. These endproducts have been shown to be responsible for many of the complications associated with diabetes.

An UF of 3 was used to account for laboratory animal-to-human interspecies differences. This UF accounts for differences in the toxicokinetics and toxicodynamics between the model species and humans. The data indicate that the toxicokinetics in the rat and humans are similar and that both species eliminate acetone from the body efficiently (Haggard et al., 1944; Sakami, 1950; Sakami and Lafaye, 1951; Stewart et al., 1975; Reichard et al., 1979; Casazza et al., 1984; Wigaeus et al., 1981; Kosugi et al., 1986a; Wang et al., 1994). In both humans and rodents metabolism proceeds by a hepatic pathway at low concentrations and by an extrahepatic pathway followed by excretion at higher concentrations but qualitative toxicokinetic comparisons between rats and humans are not available (Haggard et al., 1944; Casazza et al., 1984; Wigaeus et al., 1981; Kosugi et al., 1986b; Gavino et al., 1987; Kawai et al., 1992). Thus, the toxicokinetic component of the UF for interspecies extrapolation is 3. The critical effects identified from the principal study are kidney-related (Dietz et al., 1991; NTP, 1991). Male rats given the two highest doses of acetone had increases in the incidence and severity of nephropathy; the severity rating increased from minimal at low doses to mild at high doses. It is not known with certainty whether the observed nephropathy is a result of male rat-specific hyaline droplet formation due to α_{2u} -globulin accumulating protein (see Section 5.1.3 of the Toxicological Review). However, nephropathy was observed in all treatment groups including controls. The authors report that the effects are morphologically similar to the spontaneously occurring and long-term progression of nephropathy (chronic progressive nephropathy) found among aging rats. Acetone exposure may serve to enhance this effect. However, the nephropathy was increased only from a severity rating of "1, minimal" to "2, mild" on a scale of 1 to 5. For these reasons, the toxicodynamic component of the UF for interspecies extrapolation is 1 indicating that humans are not anticipated to be more susceptible than animals to the nephrotoxic effects of acetone exposure.

An UF of 3 was used to account for extrapolation from subchronic studies to chronic exposure conditions. The principal study is a subchronic study. No chronic studies are available. However, acetone is endogenously produced in the human body. Several reports note the presence of acetone in normal nonfasting individuals indicating that humans are routinely

exposed to acetone (Stewart et al., 1975; Physicians Desk Reference, 1976; Wang et al., 1994). Toxicokinetic studies in both humans and animals indicate that acetone elimination occurs through excretion, exhalation and metabolism by various routes. In addition, acetone does not accumulate in the body nor are its metabolites considered significantly toxic. Acetone is metabolized to acetol which in turn, is metabolized via two potential pathways to glucose. Intermediates include methylglyoxal, 1,2-propanediol, lactaldehyde, and lactate, none which have been demonstrated to be overtly toxic.

An UF of 10 was used to account for database uncertainty. The available database for acetone includes subchronic gavage and drinking water studies in mice and rats, including measurements of several reproductive parameters. There is one neurotoxicity study in rats which evaluated effects on nerve conduction velocity and rotarod performance and one reproductive toxicity study with a single dose regimen. The database lacks a multigenerational study and adequate studies of the oral neurotoxicity, developmental and developmental neurotoxicity of acetone.

The only available neurotoxicity study in mice demonstrates no effects on nerve conductivity and rotarod performance. Nevertheless, human inhalation studies on acetone, while inadequate, indicate potential neurotoxic effects. This raises concern for neurodevelopmental effects from oral exposure because the nervous system undergoes developmental processes unique to early life stages.

There are no developmental toxicity studies for acetone by the oral route of exposure; however, information on this endpoint is possibly informed by inhalation studies and studies on isopropanol. Inhalation studies on acetone reported a slight increase in the incidence of skeletal malformations in rats, although the types of malformations did not demonstrate a consistent effect. The most consistent finding was decreased fetal weight that was not associated with any other observable adverse effect (Mast et al., 1988). Developmental toxicity studies on isopropanol following gavage administration to rats and rabbits indicated reduced fetal weight at doses of 800 and 1200 mg/kg-day but no other effects at any dose (Tyl et al., 1994). In addition, a two-generation gavage study on isopropanol in rats (Bevan et al., 1995) indicated a statistically significant reduction in the P2, but not P1, male mating index at 1,000 mg/kg-day that the study authors characterized as slightly below historical controls. On the other hand, a developmental neurotoxicity study (Bates et al., 1994) on isopropanol in rats indicated no toxicity at doses as high as 1,200 mg/kg-day. It is difficult to draw firm conclusions on the potential developmental effects from oral exposure to acetone based on inhalation studies following acetone exposure and oral studies using isopropanol. However, evaluated collectively, the data may indicate potential developmental and reproductive effects resulting from ingestion of acetone.

The RfD is based on a NOAEL which obviates the need for an UF due to LOAEL to NOAEL extrapolation.

The RfD is applied to ingested acetone only and is in addition to the acetone formed endogenously by catabolism of fat. The turnover rate (mg/kg-day) for the endogenous production of acetone under normal conditions is not known.

MF =1. A modifying factor is not needed.

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

Effects from oral exposure to acetone in humans are limited to case reports. In one case report, a 17-month-old girl was given approximately 4.88 mL/kg (3,850 mg/kg bolus dose) of acetone through her gastrostomy tube (Herman et al., 1997). The child was found gagging, unresponsive, and diaphoretic with dilated sluggish pupils, right arm tonic-clonic activity, and left eye deviation, and she was unresponsive to verbal or painful stimuli. Serum ketones were still present at a 1:32 dilution and the abdomen was distended and firm. Following intubation and supportive therapy, the child recovered fully. Another case report described a 53-year-old woman admitted to the hospital after ingestion of nail polish remover (Ramu et al., 1978). Vital signs were generally normal, but neurological examination showed that even though she was oriented, the patient was lethargic but arousable and had a shortened attention span. Her blood acetone concentration was 0.25 g/dL. The woman was admitted for observation and her condition gradually improved as blood acetone levels declined.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Medium

RfD — Medium

The overall confidence in this RfD assessment is medium since both males and females were used and an extensive number of parameters were measured. It is supported by a second oral study which reported similar effects; however, the confidence is not high because the study is a subchronic rather than a chronic study. Confidence in the database is rated medium because of the availability of two oral subchronic studies in mice and rats, and extensive knowledge of the pharmacokinetic parameters; however the database lacks chronic, developmental,

developmental neurotoxicity, and multigenerational studies and adequate neurotoxicity studies. The overall confidence in this RfD assessment is medium.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

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

Source Document - U.S. EPA, 2003

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 U.S. EPA, 2003. [To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition \(PDF\)](#)

Agency Consensus Date - 05/29/2003

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 — Acetone

CASRN — 67-64-1

Last Revised — 07/31/2003

Several controlled and cohort studies from inhalation exposure to acetone are available. Dick et al. (1988) reported effects from short-term exposure to 250 ppm acetone including a mild statistically significant increase in dual task performance measurements and in the identification of false alarms during and immediately following exposure. Other neurological measurements demonstrated no treatment-related effects. In a cohort study of workers occupationally exposed to acetone at levels exceeding 500 ppm, Satoh et al. (1996) found an increase in reports of eye irritation and nausea compared with a nonexposed control cohort.

The authors speculate that the reports may be the result of peak exposures during the course of the day. They found no differences between the exposed and nonexposed cohort for the Manifest Anxiety scale or the Self-rating Depression scale. The only reported neurological effect was a statistically significant decrease in simple reaction time and digit span among workers aged 30-44. No differences were reported in workers in younger and older age groups. The study authors questioned whether the differences in only one age group were chance findings. Kiesswetter et al. (1994) report in a study of workers exposed to acetone concentrations of 725 and 1,150 ppm during the morning and afternoon shifts, respectively, that the only category of well-being related to exposure of acetone was in the "annoyance" category.

In a cohort study, 71 factory workers with mean age and length of exposure of 36 and 14 years, respectively, were evaluated for both central and peripheral nervous system effects (Mitran et al., 1997). Exposure concentrations over an 8-hour shift ranged from 416 to 890 ppm acetone. Mood disorders, irritability, memory difficulties, sleep disturbances, headache, numbness of the hands or feet, eye and/or nose irritation, bone, joint and/or muscle pain, nausea, and abdominal pain were reported slightly more frequently in exposed workers as compared with controls. The time during the work shift when the symptoms occurred or were reported was not stated. Although the results of motor nerve conduction tests on the median, ulnar and peroneal nerves indicated statistically significant reductions in latency, amplitude and/or duration of both proximal and distal responses, no consistent pattern of effect was observed. Statistically significant reductions in nerve conduction velocity in all nerves studied was reported in exposed workers as compared with controls. For the exposed workers, statistically significant delays in reaction time were observed for the visual test and a lower mean distributive attention score when compared with the controls.

The Mitran et al. (1997) study presents minimal information which confounds a meaningful appraisal of the study design. This includes a lack of information regarding the selection of controls, parameters used for age-matching and other variables, experimental procedures, i.e., blind versus nonblind determinations, and temperature control. Age-matching and consistent temperature control are known critical parameters in nerve conduction velocity measurements. Additional potential confounding issues associated with this study include no establishment of a dose-response relationship, and an inability to rule out coexposure to other toxins as the factory was a coin and metal plant where exposure to other toxins might be considered likely. Some of these issues are discussed in Boyes and Herr (2002). For these reasons, the study is not considered appropriate for the establishment of an RfC for acetone.

Stewart et al. (1975) exposed 20 adults of both sexes to acetone vapor concentrations of 0, 200, 1,000, 1,250 ppm or varying concentrations (males) and 0 or 1,000 ppm (females) for either 3½ or 7 hours for 4 days/week on successive weeks. One of four subjects exposed to

1,000 ppm and two of four subjects exposed to 1,250 ppm for 7 hours demonstrated a statistically significant effect on the visual evoked response. The effect was reported following either two or four successive days of exposure. The exposure regime indicates that the exposure duration at each concentration did not extend beyond 4 days for each dose with a 3 day interim period without dosing. While this study may be appropriate for establishing exposure limits for short-term exposure, it is not suitable for deriving a reference value for chronic exposure.

Mast et al. (1988) conducted developmental studies in rats and mice by the inhalation route of exposure. Statistically significant decreases in maternal weight and weight gain in rats were observed at the highest (11,000 ppm) exposure when compared with the controls. The effect was not observed in mice. The authors reported that there were no overt signs of developmental toxicity in either rats or mice. There were single incidences of fetal abnormalities in the high-exposure rats. Statistically significant changes in the incidence of fetal malformations in mice were not observed following exposure at any level with the exception of an increase in the percent of fetuses (on a litter basis) with reduced ossification of the sternebrae. The authors stated that this might not be biologically significant since the incidence was <10%. The offspring of rats and mice had a small, but statistically significant increase in late term resorptions compared with controls but the increase was not considered to be enough to account for a reduction in live fetuses. Similarly, there was a small but statistically significant decrease in fetal weight of offspring in both rats and mice as described by the study authors. The significance of the fetal body weight effect is questioned in light of the minimal severity of the effect, and the negative findings of other parameters including resorptions, number of live births, and number of births per litter, which were comparable to controls.

Overall, the most pronounced effect of acetone reported in human inhalation studies is irritation of the eyes and respiratory tract. Additionally, human data indicate that exposure to acetone may produce neurobehavioral effects. Studies that report responses over time note that the most pronounced effects occur during initial exposure and dissipate over time. Similarly, animal data also indicate that neurological effects from less than lifetime inhalation exposure are mild and transient. Although the available database may be sufficient to support concerns for short-term exposure (based largely on irritation) extrapolation to chronic exposure is not recommended. Available human and animal studies on acetone exposure provide insufficient information for the generation of an RfC. The available PBPK models are not amenable for route-to-route extrapolation from the oral route to the inhalation route of exposure since the oral exposure models have not been validated.

I.B.1. Inhalation RfC Summary

No RfC is recommended at this time. Available human and animal studies on exposure to acetone provide insufficient information for the generation of an RfC. The previous IRIS assessment on acetone did not derive an RfC.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Not applicable.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

Not applicable.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Not applicable.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

I.B.5. Confidence in the Inhalation RfC

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#)

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2003

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 U.S. EPA, 2003. *[To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition \(PDF\)](#)*

Agency Consensus Date - 05/29/2003

I.B.7. EPA Contacts (Inhalation RfC)

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).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Acetone

CASRN — 67-64-1

Last Revised — 07/31/2003

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 inhalation exposure. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999. Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July. Risk Assessment Forum. <http://www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm>). The quantitative risk estimates result from application of a low-dose extrapolation procedure, and both the central estimate and upper bound estimate of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways to facilitate their use. The oral slope factor is the 95% upper bound on the estimate of risk per (mg/kg)/day of oral exposure. The unit risk is the 95% upper bound on the estimate of risk, either per $\mu\text{g/L}$ drinking water or per $\mu\text{g}/\text{cu.m}$ air breathed. The third form in which risk is presented is the 95% lower bound on the estimated 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.

II.A. Evidence for Human Carcinogenicity

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

In accordance with the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999) *data are inadequate for an assessment of the human carcinogenic potential* of acetone.

This weight-of-evidence determination is based on the availability of one human study of limited utility, no chronic animal studies, and no additional information on structural analogues with known carcinogenic potential. Acetone has tested negative in almost all genotoxicity studies. The previous IRIS assessment included a weight-of-evidence classification of Group D - not classifiable as to human carcinogenicity - based on the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986).

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

II.A.2. Human Carcinogenicity Data

Inadequate.

Acetone has a long history of industrial use as a solvent. To date there are no epidemiological studies demonstrating an association between exposure to acetone and increased risk of cancer. The only human study available is an epidemiological study of workers in a cellulose acetate plant where the workers were exposed to acetone concentrations of 380-1,070 ppm (time-weighted average) (Ott et al., 1983a,b). In this study, 948 workers served as the reference cohort for a comparison to workers exposed to a mixture of methylene chloride and acetone. 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 for men and 6.7 for women. Among the acetone-exposed workers the incidence of "malignant neoplasms" was 5 and 2 compared with an expected incidence of 10 and 2.3 for men and women, respectively. Limitations of this study are discussed in Section 4.1.1 of the Toxicological Review.

II.A.3. Animal Carcinogenicity Data

Inadequate.

Although a chronic bioassay has not been conducted for oral or inhalation exposure routes, acetone has frequently been used as a solvent or vehicle control to dissolve test chemicals in dermal studies in animals (NTP, 1991, 1995, 1997) with no evidence of increased tumor incidence; however, without a naive control the ability to determine the background incidence of cancer following these exposures is limited. Chronic and less than lifetime studies on methylglyoxal, a potential metabolite of acetone, reported no signs of cancer in rats, although

both studies are limited by methodology and reporting (Fujita et al., 1986; Takahashi et al., 1989).

II.A.4. Supporting Data for Carcinogenicity

The genotoxicity of acetone has been well studied in *in vitro* assays, with the results almost entirely negative (ATSDR, 1994; OECD, 1998; U.S. EPA, 1988; WHO, 1998). All studies cited in the GENE-TOX database were negative, with the exception of one study for which no conclusion was drawn.

Neither sister chromatid exchange (SCE) 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). Acetone was also negative for inducing sister chromatid exchanges in human (Tucker et al., 1993) and nonhuman (Latt et al., 1981) cell types in the absence of metabolic activation. Acetone did not induce chromosome aberrations *in vitro* (Preston et al., 1981).

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%) inhibited background synthesis in a concentration-related manner (Lake et al., 1978). The chemical was negative for reverse mutations at concentrations up to 10 mg/plate in the Ames reversion test with five strains of *Salmonella typhimurium* in the presence or absence of a metabolic activation system (NTP, 1991; Kier et al., 1986; De Flora et al., 1984). Cell transformation was not seen in Syrian hamster embryo cells at acetone concentrations up to 8% (Heidelberger et al., 1983). Acetone was not mutagenic to *Arabidopsis* at concentrations up to 500 mM (Rédei, 1982). Male and female hamsters did not show an increase in micronuclei in polychromatic erythrocytes in the bone marrow following injection with 865 mg/kg (Basler, 1986).

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.

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

Not applicable.

II.B.1. Summary of Risk Estimates

Not applicable.

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Not applicable.

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

Not applicable.

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Not applicable.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Not applicable.

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

II.D.1. EPA Documentation

Source Document - U.S. EPA, 2003

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 U.S. EPA, 2003. [*To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition \(PDF\).*](#)

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

Agency Consensus Date - 05/29/2003

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 — Acetone
CASRN — 67-64-1

VI.A. Oral RfD References

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VII. Revision History

Substance Name — Acetone
CASRN — 67-64-1

Date	Section	Description
07/01/1990	II.	Carcinogen assessment on-line
07/31/2003	I.A.	Oral RfD updated.
07/31/2003	I.B.	Inhalation RfC discussion added.
07/31/2003	II.	Cancer assessment updated.

VIII. Synonyms

Substance Name — Acetone
CASRN — 67-64-1
Last Revised — 07/31/2003

- 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