TOXICITY SUMMARY FOR ACENAPHTHENE

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EXECUTIVE SUMMARY

Acenaphthene, also known as 1,2-dihydroacenaphthylene or 1,8-ethylenenaphthalene, is a tricyclic aromatic hydrocarbon that occurs in coal tar. It is used as a dye intermediate, in the manufacture of some plastics, and as an insecticide and fungicide (U.S. EPA, 1980). Acenaphthene has been detected in cigarette smoke, automobile exhausts, and urban air; in effluents from petrochemical, pesticide, and wood preservative industries (U.S. EPA, 1980); and in soils, groundwater, and surface waters at hazardous waste sites (ATSDR, 1990).

No absorption data are available for acenaphthene; however, by analogy to structurally-related PAHs, it would be expected to be absorbed from the gastrointestinal tract and lungs (U.S. EPA, 1988). The anhydride of naphthalic acid was identified as a urinary metabolite in rats treated orally with acenaphthene (Chang and Young, 1943).

Although a large body of literature exists on the toxicity and carcinogenicity of polycyclic aromatic hydrocarbons (PAHs), primarily benzo[*a*]pyrene, toxicity data for acenaphthene are very limited. Acenaphthene is irritating to the skin and mucous membranes of humans and animals (Sandmeyer, 1981; Knobloch et al., 1969). Acute toxicity data for animals include oral LD_{50}s of 10 g/kg for rats and 2.1 g/kg for mice (Knobloch et al., 1969) and an intraperitoneal LD_{50} of 600 mg/kg for rats (Reshetyuk et al., 1970). Oral exposure of rats to daily 2-g doses of acenaphthene for 32 days produced peripheral blood changes, mild liver and kidney damage, and pulmonary effects (Knobloch et al., 1969). Subchronic oral exposure to acenaphthene at doses of $ 350 mg/kg for 90 days produced increased liver weights, hepatocellular hypertrophy, and increased cholesterol levels in mice. Reproductive effects included decreased ovary weights at doses of $ 350 mg/kg and decreased ovarian and uterine activity as well as smaller and fewer corpora lutea at 700 mg/kg/day (U.S. EPA, 1989). Adverse effects on the blood, lungs, and glandular tissues were reported in rats exposed daily to 12 mg/m^3 of acenaphthene for 5 months (Reshetyuk et al., 1970).

A Reference Dose (RfD) of 6E-1 mg/kg/day for subchronic oral exposure (U.S. EPA, 1993a) and 6.E-2 mg/kg/day for chronic oral exposure to acenaphthene (U.S. EPA, 1993b) was calculated from a no-observed-adverse-effect level (NOAEL) of 175 mg/kg/day from a 90-day gavage study with mice. The critical effect was hepatotoxicity. Data were insufficient to derive an inhalation Reference Concentration (RfC) for acenaphthene (U.S. EPA, 1993a,b).

No oral bioassays were available to assess the carcinogenicity of acenaphthene. A limited inhalation study in which rats were exposed to 12 mg/m^3 acenaphthene for 5 months and observed an additional 8 months provided no evidence of carcinogenicity (Reshetyuk et al., 1970). EPA has not assigned a weight-of-evidence classification for carcinogenicity to acenaphthene (U.S. EPA 1993a,b).

1. INTRODUCTION

Acenaphthene (CAS Reg. No. 83-32-9), also known as 1,2-dihydroacenaphthylene or 1,8-ethylenenaphthalene, is a tricyclic aromatic hydrocarbon with a chemical formula of $C_{12}H_{10}$ and a molecular weight of 154.21 (Budavari et al., 1989). It is a crystalline solid with a boiling point of 279°C, a melting point of 95°C, and a density of 1.189 g/mL. Acenaphthene is insoluble in water, but is soluble in ethanol, methanol, propanol, chloroform, benzene, toluene, and glacial acetic acid (Budavari et al., 1989). It has a vapor pressure of 4.47×10^{-3} mm Hg (ATSDR, 1990) and a log octanol/water coefficient of 3.92-5.07 (Enzminger and Ahlert, 1987).

Acenaphthene occurs in coal tar produced during the high temperature carbonization or coking of coal. It is used as a dye intermediate, in the manufacture of some plastics, and as an insecticide and fungicide (U.S. EPA, 1980). Acenaphthene is an environmental pollutant and has been detected in cigarette smoke, automobile exhausts, and urban air; in effluents from petrochemical, pesticide, and wood preservative industries (U.S. EPA, 1980); and in soils, groundwater, and surface waters at hazardous waste sites (ATSDR, 1990). The compound is one of a number of polycyclic aromatic hydrocarbons (PAHs) on EPA's priority pollutant list (ATSDR, 1990).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

Data regarding the gastrointestinal or pulmonary absorption of acenaphthene in humans or animals were not available. However, data from structurally-related PAHs suggest that acenaphthene would be absorbed readily from the gastrointestinal tract and lungs (U.S. EPA, 1988).

2.2. DISTRIBUTION

No human or animal data were available concerning the tissue distribution of acenaphthene.

2.3. METABOLISM

Chang and Young (1943) isolated the anhydride of naphthalic acid (naphthalene-1,8-dicarboxylic acid) from the urine of male white rats fed a diet containing 1% acenaphthene (total dose 4.1 g) or dosed by gavage with a suspension of 0.1 g acenaphthene on alternate days (total dose 1.8 g), suggesting that the 5-membered ring in acenaphthene undergoes cleavage.

2.4. EXCRETION

Following oral dosing with acenaphthene, Chang and Young (1943) identified the anhydride of naphthalic acid in the urine of rats. The parent compound was not detected. No other data were available on the excretion of acenaphthene.

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Information on the acute oral toxicity of acenaphthene in humans was not available. Lillard and Powers (1975) investigated the reaction of humans to an odor from an aqueous solution of acenaphthene that could result in rejection of contaminated water. The lowest levels eliciting human responses ranged from 0.022 to 0.22 ppm.

3.1.1.2. Animal

Knobloch et al. (1969) determined oral LD_{50}s of 10 g/kg and 2.1 g/kg for rats and mice, respectively. Young rats given daily doses of 2 g/kg of acenaphthene in olive oil for 32 days exhibited loss of body weight, peripheral blood changes (unspecified), increased aminotransferase levels in blood

serum, and mild morphological damage to the liver and kidneys. At the end of the treatment period, mild bronchitis and localized inflammation of the bronchial tissue was observed (Knobloch et al., 1969).

Gershbein (1975) examined the effect of acenaphthene on the extent of liver regeneration as an indicator of the ability to induce a proliferative response in partially hepatectomized rats. Daily administration of a diet containing 0.1% acenaphthene for 10 days produced a statistically significant ($p<0.01$) increase in the extent of liver regeneration compared with controls. This effect was not observed when rats were fed a diet containing 0.03% acenaphthene for 10 days.

3.1.2. Subchronic Toxicity
3.1.2.1. Human

Information on the subchronic oral toxicity of acenaphthene in humans was not available.

3.1.2.2. Animal

In a subchronic gavage study, male and female CD-1 mice were administered 0, 175, 350, or 700 mg/kg/day of acenaphthene for 90 days (U.S. EPA, 1989). There were no treatment-related effects on survival, body weight, or total food intake. No clinical signs of toxicity or ophthalmologic alterations were observed. Statistically significant ($p\#0.05$) increases in liver weights accompanied by microscopic alteration (cellular hypertrophy) occurred in mid- and high-dosed rats (both sexes). Additionally, high-dosed males and mid- and high-dosed females had significantly ($p\#0.05$) increased cholesterol levels. In females, acenaphthene elicited adverse effects on the reproductive system characterized by decreased ovary weights (mid- and high-dosed mice, $p\#0.05$), and decreased activity of the ovaries and uterus, as well as fewer and smaller corpora lutea (high-dosed mice). Although increased liver weights, without accompanying microscopic alterations or increased cholesterol levels were also observed at the low dose, this change was considered to be adaptive rather than adverse, providing a lowest-observed-adverse-effect level (LOAEL) of 350 mg/kg/day and a no-observed-adverse-effect level (NOAEL) of 175 mg/kg/day.

3.1.3. Chronic Toxicity

Information on the chronic oral toxicity of acenaphthene in humans or animals was not available.

3.1.4. Developmental and Reproductive Toxicity
3.1.4.1. Human

Information on the developmental and reproductive toxicity of acenaphthene in humans following oral exposure was not available.

3.1.4.2. Animal

Decreased ovary weights were seen in female CD-1 mice administered 350 or 700 mg/kg/day of acenaphthene by gavage for 90 days (see also Section 3.1.2.2.). In addition, mice exposed to 700 mg/kg/day exhibited decreased ovarian and uterine activity as well as smaller and fewer corpora lutea (U.S. EPA, 1989).

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3.1.5. Reference Dose
3.1.5.1. Subchronic

ORAL RfD: 6E-1 mg/kg/day (U.S. EPA, 1993a)
NOAEL: 175 mg/kg/day
LOAEL: 350 mg/kg/day
UNCERTAINTY FACTOR: 300

PRINCIPAL STUDY: U.S. EPA, 1989

COMMENTS: The same study, described in Section 3.1.2.2, was used for the derivation of the subchronic and chronic RfD. An uncertainty factor of 300 reflects 10 each for intra- and interspecies variability and 3 for lack of adequate data in a second species and lack of reproductive/developmental toxicity studies.

3.1.5.2. Chronic

ORAL RfD: 6E-2 mg/kg/day (U.S. EPA, 1993b)
NOAEL: 175 mg/kg/day
LOAEL: 350 mg/kg/day
UNCERTAINTY FACTOR: 3000

CONFIDENCE:
Study: Low
Data Base: Low
RfD: Low

VERIFICATION DATE: 11/15/89

PRINCIPAL STUDY: U.S. EPA, 1989

COMMENTS: The RfD is based on a 90-day gavage study with mice described in Section 3.1.2.2, with hepatotoxicity as the critical effect. An uncertainty factor of 3000 reflects 10 each for intra- and interspecies variability, 10 for the use of a subchronic study for the derivation of a chronic RfD, and 3 for lack of adequate data in a second species and lack of reproductive/developmental toxicity studies.

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

Information on the acute toxicity of acenaphthene in humans or animals following inhalation exposure was not available.

3.2.2. Subchronic Toxicity

3.2.2.1. Human

Information on the subchronic toxicity of acenaphthene in humans following inhalation exposure was not available.

3.2.2.2. Animal

Adverse effects on the blood, glandular tissues (no details provided), and lungs were reported in rats exposed by inhalation to 12 mg/m^3 acenaphthene, 4 hr/day, 6 days/week for 5 months (Reshetyuk et al., 1970). Effects on the lungs included hyperplasia and metaplasia of the bronchial epithelium, which may have been the result of the pneumonia that killed many animals.

3.2.3. Chronic Toxicity

Information on the chronic toxicity of acenaphthene in humans or animals following inhalation exposure was not available.

3.2.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of acenaphthene in humans or animals following inhalation exposure was not available.

3.2.5. Reference Concentration

Data were insufficient to derive a subchronic or chronic inhalation reference concentration (RfC) for acenaphthene (U.S. EPA, 1993a,b).

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Humans

Acenaphthene is irritating to the skin and mucous membranes (Sandmeyer, 1981).

3.3.1.2. Animals

Acenaphthene was irritating to the skin and conjunctiva of rabbits, but was not sensitizing in guinea pigs (Knobloch et al., 1969).

Reshetyuk et al. (1970) determined an intraperitoneal LD_{50} of 600 mg/kg for rats. Acenaphthene in peanut oil injected subcutaneously into partially hepatectomized rats (total dose 5-20 mmol/kg) daily for 10 days produced a statistically significant ($p<0.01$) increase in liver regeneration compared with controls (Gershbein, 1975). An increase in the synthesis of liver protein was observed in rats following an intraperitoneal injection of acenaphthene at a concentration equimolar to 1 mg of 20-methylcholanthrene (0.57 mg acenaphthene) (Arcos et al., 1961).

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of acenaphthene by other routes of exposure in humans or animals was not available.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of acenaphthene by other routes of exposure in humans or animals was not available.

3.3.4. Developmental and Reproductive Toxicity

Information on the developmental or reproductive toxicity of acenaphthene by other routes of exposure in humans or animals was not available.

3.4. TARGET ORGANS/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target Organs

1. Liver. Subchronic oral exposure of rats to acenaphthene produced increased liver weights, hepatocellular hypertrophy, and increased cholesterol levels. Mild morphological liver changes were seen in rats following subacute exposure.

2. Reproductive System. Subchronic oral exposure of rats to acenaphthene produced decreased ovary weights, inactivity of the ovaries and uterus, and fewer and smaller corpora lutea.

3.4.1.2. Other Target Organs

Information concerning other target organs following oral exposure to acenaphthene was not available.

3.4.2. Inhalation Exposures
3.4.2.1. Primary Target Organs

The available data were inadequate to determine primary target organs for inhalation exposure to acenaphthene.

3.4.2.2. Other Target Organs

1. Lungs. Pneumonia with hyperplasia and metaplasia of the bronchial epithelium was reported in rats subchronically exposed to acenaphthene.

2. Blood. Subchronic exposure produced unspecified hematologic effects in rats.

3.4.3. Other Routes of Exposure

Skin. Acenaphthene is irritating to the skin and mucous membranes.

4. CARCINOGENICITY
4.1. ORAL EXPOSURES

Information on the carcinogenicity of acenaphthene in humans or animals following oral exposure was not available.

4.2. INHALATION EXPOSURES
4.2.1. Human

Information on the carcinogenicity of acenaphthene in humans following inhalation exposure was not available.

4.2.2. Animal

Reshetyuk et al. (1970) exposed rats by inhalation to 12 mg/m^3 acenaphthene, 4 hr/day, 6 days/week for 5 months. Although the bronchial epithelium showed hyperplasia and metaplasia, no signs of malignancy appeared during the 8-month observation period.

4.3. OTHER ROUTES OF EXPOSURE
4.3.1. Human

Information on the carcinogenicity of acenaphthene in humans by other routes of exposure was not available.

4.3.2. Animal

Negative results were reported in a short-term predictive test for carcinogenicity in which newts (*Triturus cristatus*) were injected subcutaneously with acenaphthene (dose not reported) (Neukomm, 1974).

Akin et al. (1976) isolated some PAH-rich fractions of cigarette smoke condensate and tested them for tumor promotion on mouse skin. Female mice received an application of 125 µg 7,12-dimethylbenz[*a*]anthracene (DMBA) as initiator; 3-4 weeks later the smoke condensate fraction (containing acenaphthene and other PAHs) was applied 5 times weekly for 13 months. Compared with controls treated with DMBA and acetone, the fraction containing acenaphthene elicited no significant tumor-promoting activity.

To examine the effect of acenaphthene on a liver microsomal enzyme, dimethylnitrosamine demethylase, the enzyme that demethylates the known carcinogen dimethylnitrosamine (DMN), Arcos et al. (1976) injected male weanling rats intraperitoneally with acenaphthene at concentrations equimolar to 40 mg of 20-methylcholanthrene (23 mg acenaphthene). After 24 hr, treated rats showed a 5% decrease

of enzyme activity compared with controls. The investigators noted that demethylation is a requirement for carcinogenesis by DNM, and, thus, it is possible that acenaphthene may slightly inhibit DMN carcinogenesis.

4.4. EPA WEIGHT-OF-EVIDENCE

A weight-of-evidence classification for acenaphthene is not listed in HEAST (U.S. EPA, 1993a) or IRIS (U.S. EPA, 1993b).

4.5. CARCINOGENICITY SLOPE FACTORS

None were calculated.

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