



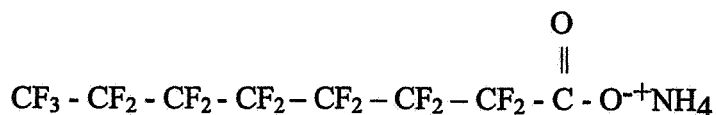
HASKELL LABORATORY

Common Name: Ammonium Perfluorooctanoate (C-8)

Chemical Name: Octanoic acid, pentadecafluoro-, ammonium salt

CAS Registry No.: 3825-26-1

Chemical Structure:



Physical Properties:

Form:	White powder
Molecular Weight:	431
Boiling Point:	Sublimes @ 110°C
Melting Point:	----
Density:	----

Drinking Water Guideline (CEG_w)

1 ug/L

General Toxicity

Ammonium perfluorooctanoate (C-8) has moderate acute oral toxicity with an LD50 in rats of 470 mg/kg [REDACTED] (1981b). An aqueous paste of C-8 produced mild to moderate irritation on the skin of rabbits [REDACTED] (1979c). Clinical signs of toxicity including weight loss and labored breathing occurred at doses as low as 1500 mg/kg [REDACTED] (1979d). Instillation of the solid into the rabbit eye produced moderate corneal opacity, iritis, and conjunctivitis. The ocular effects gradually receded. Prompt washing of the treated eye reduced the degree of injury and the washed eye recovered more quickly [REDACTED] (1979b). By the acute inhalation route, C-8 has a four-hour ALC in the rat of 800 mg/m³ [REDACTED] (1969).

Clinical Human Studies

Perfluorooctanoic acid (PFOA) has a long half-life in humans. A study of occupationally exposed workers at a plant which produces C-8 showed organic fluorine levels in the blood ranging from 1 to 71 ppm. One worker with a level of 70 ppm was removed from the fluoro-chemical production area and his blood analyzed for organic fluorine over several months. After 18 months, his organic fluorine level had decreased only to 39 ppm [45% reduction] (Ubel et al., 1980). Serum PFOA levels were again measured in 1993, 1995, and in 1997. Serum PFOA levels by year were: 1993 [mean 5.0 ppm, range 0-80.0 ppm]; 1995 [mean 6.8 ppm, range 0-114.1 ppm]; and 1997 [mean 6.4 ppm, range 0.1-81.3 ppm].

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In the 1997 examination, there was no evidence of abnormal liver function tests, hypolipidemia, or cholestasis associated with these PFOA levels (██████████, 2000). Similar results were seen in an earlier study of 115 workers; serum PFOA levels varied between 0 and 26 ppm with a mean of 3.3 ppm (Gilliland and Mandel, 1996).

A study was made of Washington Works employees potentially exposed to C-8. Results of blood chemistry testing (SGOT, LDH, AP, and bilirubin) indicated no conclusive evidence of an occupationally-related health problem among workers exposed to C-8 (██████████ 1981d).

Perfluorooctanoic acid (PFOA), a peroxisome proliferator, has produced a dose-related increase in hepatic, pancreatic acinar, and Leydig cell adenomas in rats. In addition, PFOA increased serum estradiol levels through the induction of hepatic aromatase activity. In 1993 and 1995, two cross-sectional studies of 111 and 80 production workers, respectively, were conducted to measure their serum PFOA in relation to several reproductive hormones to determine whether such an effect occurs in humans. PFOA was not significantly associated with estradiol or testosterone in either year's study. A 10% increase in mean estradiol levels was observed among employees who had the highest levels of serum PFOA, although this association was confounded by body mass index (Olsen et al., 1998).

Extended Studies in Animals

In a two-week study, groups of rats were exposed to 11 or 83 mg/m³ of C-8. Liver degeneration, enlarged livers, and increases in liver enzymes were observed in both groups (██████████ 1979a). A second two-week study was conducted with exposure levels of 1, 7.6, and 83.9 mg/m³. Mortality occurred at the highest exposure level. Liver changes were noted in the rats exposed to 7.6 and 83.9 mg/m³. These liver changes appeared to be reversible (██████████ 1981a). Subchronic studies by the oral and dermal routes confirm the effect of C-8 on the liver (██████████ 1980; Griffith and Long, 1980).

Groups of male Rhesus monkeys were administered capsules containing 3, 10, or 30 mg/kg/day for up to 6 months. The high dose was reduced to 20 mg/kg/day on day 22 of the study and this dose was administered until the end of the study for 3 monkeys; 2 others had dosing discontinued from days 43 to 81 and one monkey died on day 29. One monkey in the low-dose group also died but the cause of death was unclear. No clinical signs of toxicity were seen in the 3 or 10 mg/kg/day groups. Monkeys administered 30 mg/kg/day lost weight and had low food consumption. After reducing the dose to 20 mg/kg/day, these monkeys still ate less than controls but the marked weight loss was not seen; however, the weight gain of these monkeys was less than that of the controls. No clinical signs of toxicity were seen in 2/5 monkeys after the dose was reduced. Liver weights were increased in all dosed monkeys but no pathological liver changes were seen. Additionally, no hormonal changes were seen in any of the dosed monkeys. C-8 levels in the liver were proportional to the administered dose. Blood levels of C-8 quickly reached a plateau level during dosing and were also quickly reduced after dosing stopped. Urinary levels of C-8 which were also proportional to the dose, were quickly reduced after dosing was stopped (██████████ 1999).

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Carcinogenic Potential

Groups of male and female rats were fed diets containing either 30 or 300 ppm of C-8 for two years, while a control group received only untreated feed.

The major in-life findings associated with C-8 administration consisted of: a dose dependent decrease in mean body weight gain and a treatment-related increase in food consumption in males; a slight treatment-related increase in the incidence of ataxia was observed in the females. There was no increase in mortality observed in either treatment group when compared to the control population.

C-8 related hematologic changes seen in the treated rats consisted of decreased red blood cell counts, hemoglobin, and hematocrit values seen at various times throughout the two-year test period. While the decreases in erythrocyte counts were observed very early in the study, this condition did not progress into a generalized anemia by the end of the two-year study.

Histopathologically, C-8 associated toxic changes were found in the liver. These changes were characterized by increased liver weights, increased size of the liver cells with vacuolation of the cytoplasm, and some evidence of hepatocellular degeneration with occasional signs of necrosis. As with the red blood cell findings, these liver changes were noted early in the study and showed very little evidence of progression over the remainder of the two-year study.

The incidence of tumors found in this study was relatively low and the types of neoplasms found were not different from the tumor profiles commonly found in geriatric rats. Hepatocellular tumors were very slightly increased in the high-dose male rats; however, not to the extent that would be expected considering the morphological evidence of chronic hepatocellular stimulation first seen at the one-year necropsy [REDACTED] 1987).

All of the liver tumors were carcinomas and the incidence in the control, 30 ppm, and 300 ppm groups (males: 3/50, 1/50, 5/50; females: 0/50, 0/50, 1/50) did not appear to be dose related. The incidence of nodular hyperplasia in the liver (males: 1/50, 0/50, 2/50; females: 0/50, 0/50, 3/50) was also slightly increased, though not statistically significantly [REDACTED] 1987).

All of the other remarkable tumor incidence values produced in this study were associated with endocrine or endocrine-sensitive organs [REDACTED] 1987):

- The incidence of mammary gland fibroadenomas (10/50 (20%), 19/50 (38%), 21/50 (42%)) suggested a compound-related effect. However, when compared to Haskell's historical control incidence for this strain of rat (37%), there does not appear to be any compound-related effect.
- The incidence of testicular Leydig cell adenomas (0/50 (0%), 3/50 (6%), 7/50 (14%)) was also suggestive of a compound-related effect. When compared to Haskell's control incidence for this strain of rat (6.1%, range 1-12%), the incidence in the 300 ppm group shows a statistically significant increase.

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C-8 was included in a mechanistic bioassay investigating extrahepatic tumor induction by compounds which induce peroxisome proliferation. In this study, 300 ppm of C-8 was fed to rats for two years. Increased incidences of combined (single, multiple) hepatic adenomas (10/76 versus 2/80 in *ad libitum* controls and 3/79 in pair-fed controls), Leydig cell adenomas 8/76 versus 0/79 and 2/78 in control groups), and combined pancreatic acinar cell adenomas (7/76 versus 0/80 and 1/79 in control groups) were noted. The tumor incidences were outside the historical control incidence range for Haskell Laboratory, and in addition, age-adjustment statistics also supported the conclusion that the tumor incidences were elevated for the liver, pancreas, and testis [REDACTED] 1993).

Epidemiology

In a retrospective cohort mortality study, the relationship between mortality and employment at a perfluorooctanoic acid (PFOA) production plant were investigated. The cohort consisted of 2788 male and 749 female workers employed between 1947 and 1983. The all-causes standardized mortality rate (SMR) was 0.75 for men and 0.77 for women. Among men, the cardiovascular SMR was 0.68 and the all-gastrointestinal diseases SMR was 0.57. There was no significantly increased cause-specific SMR for either men or women. The SMRs for prostate cancer were 2.03 in the Chemical Division group (exposed) and 0.58 in the non-Chemical Division group (not exposed to chemicals). In the Chemical Division group there were 4 observed and 2 expected deaths from prostate cancer. There was no significant association between any cause of death and latency in either group. In the Chemical Division group, the SMR for prostate cancer was 1.61 in the greater than 15-year latency group. For all men employed at this plant, 6 deaths were recorded for prostate cancer versus 6 expected (Gilliland and Mandel, 1993). Further examination of this cohort by a 3M epidemiologist shows no association exists between PFOA exposure and prostate cancer. [REDACTED]

Mutagenic Potential

C-8 was negative in the Ames *Salmonella* assay either in the presence or absence of a metabolic activation system. It also was negative in the yeast *Saccharomyces cerevisiae* (Griffith and Long, 1980).

Developmental Toxicity

Because an initial study in rats suggested a possible teratogenic effect (3M Co., 1981a), three studies in rats and one in rabbits were conducted. No teratogenic effects were noted in the following studies:

- Groups of pregnant rats were administered by gavage 0.05, 1.5, 50, or 150 mg/kg of C-8 on days 6-15 of gestation. Maternal toxicity occurred at 150 mg/kg. No teratogenic or embryotoxic effects were noted [REDACTED] 1981b).
- Pregnant rats were administered by gavage 100 mg/kg of C-8 on days 6-15 of gestation. Maternal toxicity was noted. A slight developmental effect related to the stress evoked by the toxic state of the dams was noted. Postpartum development, growth rate, and viability were not affected [REDACTED] 1982).

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- Groups of pregnant rabbits were administered by gavage 1.5, 5, or 50 mg/kg of C-8 in distilled water on days 6-18 of gestation. Dams administered 50 mg/kg lost weight as compared to the controls. No teratogenic effects were noted [REDACTED] 1982).
- Groups of pregnant rats were exposed by inhalation to 0.14, 1.2, 9.9, or 21 mg/m³ of C-8 on days 6-15 of gestation. Maternal toxicity was noted in the dams exposed to 9.9 and 21 mg/m³. Embryotoxicity was noted in the 21 mg/m³ group. No teratogenic effects occurred [REDACTED] 1981c).

Reproductive Toxicity

No information was available.

Basis for Community Exposure Guideline

Based on the 1 mg/m³ NOEL determined in the second two-week inhalation study, an AEL of 0.01 mg/m³ (8-hour TWA), initially recommended in 1979, was reconfirmed in 1982.

The 30 ppm dose level in the two-year feeding study was a marginal effect level for liver toxicity and a NOEL for tumorigenicity. This dose level is equivalent to 1.5 mg/kg/day for both sexes combined. Assuming 100% absorption of an inhaled dose, a 70 kg body weight, and inhalation of 10 m³ of air in an 8-hour workday, an airborne C-8 concentration of 10.5 mg/m³ would yield this dose level in a worker. Exposure at the 0.01 mg/m³ AEL would result in about a 1000-fold safety factor. Therefore, based on the 30 ppm marginal effect level for liver toxicity and the slow clearance of C-8 from human blood, no change was made in the AEL.

The 0.01 mg/m³ AEL was reduced to account for the longer exposure period (24 hours versus 8 hours), for the diverse population found in the community (the aged, the infirm, the young, etc.), and for the long half-life of C-8 in the blood. Accordingly, a CEG (air) of 0.3 ug/m³ was recommended. At this recommended 0.3 ug/m³ CEG, a maximum intake of 6 ug/day of C-8 would be realized if exposure to C-8 was only by inhalation. If exposure is possible by both consumption of drinking water and exposure to air containing C-8, this 6 ug/day maximum must be partitioned between the two routes of exposure. Therefore, assuming 20% of the 6 ug intake could come from drinking water and assuming ingestion of 2 L of drinking water per day, a CEG of 1 ug/L of water was recommended.

C-8 was updated in 1993 and the data found (mechanistic study and epidemiology results) added to the AEL documentation. Based on these additional data, the current AEL and CEG values appear appropriate and no change was recommended at this time.

C-8 was updated again in 1999 when results of an a monkey study became available. Based on increased liver weights, which might be related to enzyme induction, no NOEL was determined in this study. These data need to be further evaluated to determine the significance of this liver effect. Even if it is considered compound related, the current AEL of 0.01 mg/m³ provides a 2000x safety factor from the 3 mg/kg/day dose level. Therefore, no change was made at this time in the current AEL or CEG recommendations.

C-8 was updated again in August 2000 with the information found added to this documentation. These data do not warrant any change in the current AEL or CEG.

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1979b. [REDACTED] HL-635-79
1979c. [REDACTED] HL-636-79
1979d. [REDACTED] HL-659-79
1980. [REDACTED] HL-589-80
1981a. [REDACTED] HL-205-81
1981b. [REDACTED] HL-295-81
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[REDACTED]
June 4, 1991

Updated by:

[REDACTED] December 7, 1993, November 12, 1999, and August 24, 2000
[REDACTED]

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