Sodium fluoroacetate; CASRN 62-74-8

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 Sodium fluoroacetate

File First On-Line 05/01/1991

<table>
<thead>
<tr>
<th>Category (section)</th>
<th>Assessment Available?</th>
<th>Last Revised</th>
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<tr>
<td>Oral RfD (I.A.)</td>
<td>yes</td>
<td>05/01/1991</td>
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<tr>
<td>Inhalation RfC (I.B.)</td>
<td>not evaluated</td>
<td></td>
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<tr>
<td>Carcinogenicity Assessment (II.)</td>
<td>not evaluated</td>
<td></td>
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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Sodium fluoroacetate
CASRN — 62-74-8
Last Revised — 05/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of
information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

<table>
<thead>
<tr>
<th>Critical Effect</th>
<th>Experimental Doses*</th>
<th>UF</th>
<th>MF</th>
<th>RfD</th>
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<tbody>
<tr>
<td>Increased heart weight in females and males; decreased testis weight and altered spermatogenesis in males</td>
<td>NOAEL: 0.05 mg/kg/day</td>
<td>3000</td>
<td>1</td>
<td>2E-5 mg/kg/day</td>
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<tr>
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<td>LOAEL: 0.20 mg/kg/day</td>
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</table>

13-Week Rat Oral Study (gavage)

U.S. EPA, 1988

* Conversion Factors: None

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


Sodium fluoroacetate was administered by gavage to male and female Sprague- Dawley rats (20/sex/group) at doses of 0, 0.05, 0.20 or 0.50 mg/kg/day for 13 weeks. Individual body weight measurements, food consumption and ophthalmoscopic examination indicated no signs of toxicity. During weeks 4 and 13, blood samples were collected and examined for hematology (hemoglobin; hematocrit; leukocyte, erythrocyte, platelet, reticulocyte and differential leukocyte count; and cell morphology) and complete serum chemistry analysis including fluorocitrate measurement. Following sacrifice at week 13, all animals were necropsied, after which organ weights were recorded, tissue samples taken, and complete histopathological examinations performed. Observed dose-related effects in organ weights were: increased absolute and relative heart weight in mid- and high-dose females and high-dose males; significantly decreased absolute and relative testis weights in mid- and high-dose males; and significantly decreased absolute spleen weights in high-dose males. In mid- and high-dose males, changes in the testes included bilateral hypospermatogenesis with fusion bodies in the seminiferous tubules, and in the
epididymides, immature and/or abnormal sperm and reduced sperm count were noted. Histopathological changes in heart tissue, if any, consisted of subacute, minimal inflammation, but were not dose related. One female rat (in the high-dose group) that died before week 13 could not be classified as an accidental death. Four high-dose female rats exhibited convulsions on study day 79 (week 12), with no recurrences for the remainder of the study. Fluorocitrate levels were significantly increased after 4 weeks in the high-dose males and after 13 weeks in both the mid- and high-dose groups of both sexes. No significant hematological changes were recorded in female groups. Blood urea nitrogen was significantly decreased in low-dose males at week 4, but increased in high-dose males at week 13. High-dose females exhibited decreased total serum protein, and mid- and high-dose females had decreased globulin. The treatment-related findings of increased sodium fluorocitrate, increased heart weight, decreased testes weight with accompanying microscopic lesions of the testes, and central nervous system effects such as convulsions are consistent with those reported in the literature (discussed below). Based on increased heart weight in mid-dose females and testicular changes in mid-dose males, the LOAEL is considered to be 0.2 mg/kg/day and the NOAEL to be 0.05 mg/kg/day.

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

UF — An uncertainty factor of 3000 was used: 10 to account for interspecies extrapolation, 10 for differences in human sensitivity, 10 for use of a subchronic study for a chronic RfD derivation, and 3 for the lack of reproductive/developmental studies and toxicity studies in a second species.

MF — None

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

Sodium fluoroacetate (compound 1080) had been previously used as a potent rodenticide which has a well-characterized mechanism of action. Fluoroacetate is converted to fluorocitrate in vivo which in turn inhibits the enzyme aconitase of the tricarboxylic acid (TcA or Krebs) cycle. This enzyme converts citric acid to cis-aconitic acid/isocitric acid. The inhibition of aconitase by fluorocitrate results in a lethal accumulation of citric acid which in turn causes violent convulsions and death from cardiac failure or respiratory arrest (Gribble, 1973). Administration of an intraperitoneal dose of 5 mg sodium fluoroacetate/kg in rats 3 hours prior to liver perfusion resulted in a dramatic inhibition of TCA cycle activity. Citric acid accumulated 5-fold, glycolysis and gluconeogenesis activity decreased by 50-90% and mixed function oxidation was decreased by 50% (Zhou et al., 1984). Although administration of fluoroacetate following a single intravenous injection results in substantial bone accumulation indicative of defluorination of the molecule (Sykes et al., 1986), the acute and subchronic toxicological effects of fluoroacetate are clearly due to aconitase inhibition.
Fluoroacetate exhibits a varied pharmacological activity in different species. The LD50 ranges from 0.06 mg/kg in dogs to >500 mg/kg in the South African clawed toad. Typical LD50s of other species of common interest are: 2-5 mg/kg for humans (extrapolated value), 5.0 mg/kg for albino rats, 5-20 mg/kg for albino mice, 0.25-1.0 mg/kg for rabbits and 0.06 mg/kg for dogs. The major site of pharmacodynamic action is typically the central nervous system or the heart. Death usually results from either respiratory arrest following severe convulsions, gradual cardiac failure or ventricular fibrillation, or progressive depression of the CNS with either respiratory or cardiac failure as the terminal event. There is a general tendency for herbivores to exhibit cardiac effects, carnivores to develop CNS convulsions or depression, and omnivores to exhibit effects upon both organ systems. Tolerance to increasing doses of fluoroacetate has been demonstrated in mice, rats and the rhesus monkey, although this phenomena has not been shown in the dog or rabbit (Chenoweth, 1949). The wide range of LD50 values among the various species listed above may be due to the ability of a particular species to metabolize monofluoroacetate compounds to nontoxic metabolites. Rodents and nonhuman primates have increased tolerance to challenging doses following repeated sublethal doses of monofluoroacetate. Dogs have not shown this response. Furthermore, dogs and rabbits have been shown to accumulate monofluoroacetate following repeated sublethal doses until lethal levels are attained. Mice and rats, on the other hand, have demonstrated the ability to tolerate such a regimen possibly through a more efficient detoxification mechanism (U.S. Dept. of the Interior, 1971).

Trabes et al. (1983) has presented a case report in which a previously healthy 15-year-old female attempted suicide by ingesting sodium fluoroacetate. Nausea, vomiting and abdominal pain occurred 30 minutes after ingestion with a subsequent gran mal seizure occurring 60 minutes after the initial onset of symptoms. Over the next 4 hours, three additional gran mal seizures occurred before the patient became comatose. The patient regained consciousness after 3 days and grew progressively alert after 2 weeks. Upon neurological examination after the 2-week recovery period, severe cerebellar dysfunction with moderate diffuse brain atrophy with widening of the basal cisterns, quadrigeminal cistern, interhemispheric fissure, lateral ventricles and the third ventricle was established. By 18 months, memory disturbances and depressive behavior persisted as did a moderate cerebellar ataxia. The symptoms exhibited in human poisoning by fluoroacetate are consistent with the effects of fluorocitrate inhibition of aconitase in the cat, pig and rhesus monkey. The prolonged anoxic state of the brain in the acute phase of poisoning induced the severe CNS disabilities observed in this patient.
I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

The principal study identified both a NOAEL and a LOAEL for relevant toxicological endpoints in both genders, and is considered to be of medium confidence. The database for this compound is limited, lacking chronic and reproductive/developmental studies; low confidence in both the database and RfD follow.

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


Verification Date — 02/20/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for sodium fluoroacetate conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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

Substance Name — Sodium fluoroacetate
CASRN — 62-74-8

Not available at this time.
II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Sodium fluoroacetate
CASRN — 62-74-8

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

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III. [reserved]
IV. [reserved]
V. [reserved]

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VI. Bibliography

Substance Name — Sodium fluoroacetate
CASRN — 62-74-8

VI.A. Oral RfD References


VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Sodium fluoroacetate
CASRN — 62-74-8

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VIII. Synonyms

Substance Name — Sodium fluoroacetate
CASRN — 62-74-8
Last Revised — 05/01/1991

- 62-74-8
- Acetic acid, fluoro-, sodium salt
- Caswell No. 770
- Compound 1080
- EPA Pesticide Chemical Code 075003
- Fluocacetato de sodio [Spanish]
- Fluoracetate de sodium [French]
- Fluoressigaeure [German]
- Fluoroacetate de sodium [ISO-French]
- Fluoroacetic acid
- FLUOROACETIC ACID, SODIUM SALT
- FLUOROCTAN SODNY [Czech]
- Fratol
- Furatol
- HSDB 743
- LATKA 1080 [Czech]
- MONOFLUORESSIGSAURES NATRIUM [German]
- Natriumfluoracetaat [Dutch]
- Natriumfluoracetat [German]
- NSC 77690
- Ratbane 1080
- RCRA WASTE NUMBER P058
- SMFA
- SODIO, FLUORACETATO DI [Italian]
- Sodium fluoacetate
- SODIUM FLUOACETIC ACID
- Sodium fluoracetate
- Sodium fluoroacetate
- SODIUM FLUOROACETATE DE [French]
- Sodium monofluoroacetate
- UN 2629
- Yasoknock
- 1080