

**The Longwood Herbal Task Force**  
(<http://www.mcp.edu/herbal/default.htm>) and  
**The Center for Holistic Pediatric Education and Research**

## **Hydrazine Sulfate**

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### *Overview*

Hydrazine sulfate is an industrial chemical marketed to prevent weight loss and anorexia associated with cancer. It has not proved effective in improving appetite, reducing weight loss or improving survival in large randomized controlled trials in adults with lung or colorectal cancer. On the contrary, HS causes marked hepatotoxicity and hepatic tumors in rodents; it is associated with nausea and vomiting, fatigue, sensory and motor neuropathies and significantly reduced quality of life in cancer patients. It is currently being investigated as a potential treatment for endotoxin-mediated shock. HS has significant mutagenicity and carcinogenicity in animal studies. It has not been evaluated for safety or toxicity during pregnancy, lactation or childhood.

### *Historical and Popular Uses*

Hydrazine sulfate (HS) is a synthetic chemical used to treat solid tumors, decreased appetite, weight loss and wasting. The compound is also used in various industrial processes and is found in rocket fuel and tobacco smoke<sup>1</sup>. Dr. Joseph Gold, Director of the Cancer Research Institute in Syracuse, NY, developed the use of HS as an adjunctive cancer treatment based on its anti-gluconeogenic effects. HS interrupts gluconeogenesis by blocking phosphoenolpyruvate carboxykinase, thereby depriving tumor cells of energy needed for growth. Case reports and case series of seriously ill patients given HS offered promising testimonials about its ability to reverse cachexia and even slow or reverse tumor progression and prolong survival\*. Unfortunately, the hope initially offered by case series has not been substantiated in larger randomized, controlled

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\* One of the more well-publicized cases of using HS involved Kathy Keeton, wife of publisher Bob Guccione, who believed that Hydrazine sulfate had put her breast cancer into remission, but who subsequently died; her husband filed a class action lawsuit in 1998 against the National Cancer Institute for depriving the American public of this popular cancer remedy.

clinical trials.

### ***Botany***

Not applicable. Hydrazine sulfate is a synthetic chemical, H(6)N(2)O(4)S; its molecular weight is 130.1.

### ***Biochemistry***

Hydrazine sulfate interrupts gluconeogenesis by blocking phosphoenolpyruvate carboxykinase and is a mild monoamine oxidase (MAO) inhibitor.

## *Experimental Studies*

### **Hydrazine Sulfate: Potential Clinical Benefits**

1. Cardiovascular: none
2. Pulmonary: none
3. Renal and electrolyte balance: none
4. Gastrointestinal/hepatic: Normalization of glucose metabolism in oncology patients (see Antineoplastic)
5. Neuro-psychiatric: none
6. Endocrine: none
7. Hematologic: none
8. Rheumatologic: none
9. Reproductive: none
10. Immune modulation: none
11. Antimicrobial: none
12. Antineoplastic: Prevention and treatment of weight loss, antitumor effects
13. Antioxidant: none
14. Skin and mucus membranes: none
15. Other/miscellaneous: Treatment of endotoxic shock (experimental use)

1. **Cardiovascular:** none
2. **Pulmonary:** none
3. **Renal and electrolyte balance:** none
4. **Gastrointestinal/hepatic:** Normalization of glucose metabolism in oncology patients: see Antineoplastic section; also see Toxicity section for hepatic effects.
5. **Neuro-psychiatric:** none
6. **Endocrine:** none
7. **Hematologic:** none
8. **Rheumatologic:** none
9. **Reproductive:** none
10. **Immune modulation:** none

11. **Antimicrobial:** none

12. **Antineoplastic:** Prevention and treatment of weight loss, antitumor effects

a. Prevention and treatment of weight loss

i. *In vitro data:* none

ii. *Animal data:* In rats with hepatomas, caloric supplements alone did not prevent cachexia, but supplements combined with HS did prevent weight loss. However, tumor growth was also stimulated by the combination therapy with nutritional supplements and HS<sup>2,3</sup>.

iii. *Human data:* In pilot studies of malnourished adults with advanced solid tumors, one month of treatment with HS (60 mg TID) decreased amino acid turnover, stabilized serum albumin markers and improved glucose tolerance<sup>4,5</sup>. In a randomized, placebo controlled trial of 61 adult oncology patients suffering from weight loss, the HS-treated patients were significantly more likely than the placebo group to report improved appetite and to maintain or increase their weight; however, there was a very high drop-out rate (40% within one month)<sup>6</sup>. In a randomized, controlled trial of 127 patients with metastatic colorectal cancer, HS treatment failed to affect anorexia or weight loss; in fact, HS treatment was associated with lower survival rates and poorer quality of life<sup>7</sup>. HS appears to be ineffective in reducing cachexia compared with clinically effective medications such as corticosteroids and progestational agents such as megestrol<sup>8</sup>. Instead, the larger, controlled studies indicated that HS treatment was associated with a poorer quality of life and more side effects than placebo treatment.

b. Antitumor effects

i. *In vitro data:* Hydrazine sulfate treatment of both human and animal prostate cancer cell lines did not inhibit growth<sup>9</sup>.

ii. *Animal data:* In the mid 1970's studies in rats showed promising results when combining HS with Cytosan, mitomycin C, methotrexate and bleomycin in animals with Walker 256 carcinosarcoma<sup>10</sup>. However, in rats with prostate cancer, treatment with hydrazine sulfate did not suppress cancer growth<sup>9</sup>.

HS induced hepatic and pulmonary tumors in both treated mice and their offspring<sup>11,12,13</sup>.

iii. *Human data*: In Gold's open label, uncontrolled trial of 84 adults with a variety of disseminated tumors treated with HS, 70% of patients reported subjective improvement and 17% had objectively measurable improvements in appetite, weight, strength, pain, and tumor size; side effects included paresthesias, nausea, pruritus, fatigue and drowsiness<sup>14</sup>. In three Russian open label trials of HS (Sehydriin) in 102, 233 and 740 adults with advanced, recurrent or metastatic solid tumors for whom all other therapies had been exhausted, there were no complete remissions, but many patients reported subjective symptomatic relief, about 20% had tumor stabilization, and 10% had some tumor regression. Side effects such as dizziness, insomnia, vomiting and peripheral neuropathies were reported in 10% - 22%<sup>15,16,17</sup>. An American open label trial of HS (60 mg po TID) given to 25 adults with advanced disease demonstrated no benefits in terms of survival, tumor regression, appetite or sense of well-being<sup>18</sup>.

In a 1990 randomized trial, 65 adults with non-small-cell lung cancer were treated with standard chemotherapy and were randomized to either HS (60 mg TID) or placebo; the HS group had significantly greater caloric intake, but no significant improvement in survival<sup>19</sup>. Based on the improvements in a small subset of patients in this study, larger controlled trials were undertaken. In a double-blind, randomized, placebo-controlled trial of 291 adults with Stage IIIb or IV non-small-cell lung cancer treated with standard chemotherapy, the HS group (60mg po TID) had no clinically or statistically different outcomes in terms of survival, tumor response, weight loss, anorexia, or overall nutritional status; the HS group had significantly more sensory and motor neuropathies and significantly poorer quality of life<sup>20,21,22</sup>. In another double-blind, randomized controlled trial of 243 adults with newly-diagnosed, unresectable non-small cell lung cancer, all were treated with standard chemotherapy, and half were randomized to receive HS, while half received placebo. There were no differences in quality of life or toxicity, but there were trends toward faster disease progression and reduced survival in the HS-treated group<sup>23</sup>.

Similarly, in a randomized, placebo-controlled trial of 127 patients with metastatic colorectal cancer, the HS group had somewhat reduced survival and poorer quality of life than the placebo group; differences were not statistically significant<sup>7</sup>.

One of the researchers who reported positive results in earlier trials later concluded that HS (like other initially promising therapies such as corticosteroids, cyproheptadine and growth hormone) was ineffective in improving anthropometric parameters or clinical outcomes in cancer patients<sup>24</sup>.

13. **Antioxidant:** none

14. **Skin and mucus membranes:** none

15. **Other/miscellaneous:** Treatment of endotoxic shock

- i. *In vitro data:* In mouse macrophages, hydrazine sulfate selectively modulated the tumor necrosis factor (TNF) response to endotoxin<sup>25</sup>. HS inhibited the lytic activity of TNF (cachectin) on L-929 cells and potentiated TNF anti-viral activity<sup>26</sup>.
- ii. *Animal data:* Hydrazine sulfate protected against endotoxic shock in mice, but only in those with an intact pituitary–adrenal axis<sup>27,28,29</sup>; it apparently modifies the response to lipopolysaccharide-induced shock by modulating production of tumor necrosis factor (TNF)<sup>30</sup>. HS also appears to protect against hepatic damage induced by endotoxins in aged mice<sup>31</sup>.
- iii. *Human data:* none

## ***Toxicity and Contraindications***

*Potentially toxic compounds in hydrazine sulfate:* Hydrazine sulfate itself

*Acute toxicity:* One time low to moderate doses (10 – 40 mg/kg) of HS given intravenously to rhesus monkeys did not cause acute liver damage; however, two animals who received high doses (80 mg/kg) had extensive hepatic necrosis<sup>32</sup>. In one study of mice, a single dose of hydrazine sulfate was carcinogenic<sup>33</sup>. HS is a severe skin and mucus membrane irritant; systemic effects include weight loss, weakness and excitability. Side effects of systemic treatment have been reported in 10% - 20% of oncology patients and consist of nausea, pruritis, headache, dizziness, drowsiness, insomnia and peripheral neuropathies<sup>34</sup>.

*Chronic toxicity:* HS is mutagenic *in vitro* in studies using the standard *Salmonella typhimurium* assay<sup>35,36,37</sup>. HS is not genotoxic to mice when given in a huge one-time dose, but it is genotoxic when given in smaller doses over longer periods of time; it can induce liver tumors in rodents<sup>38,39,40</sup>. HS is carcinogenic in hamsters in a dose-dependent fashion via site-specific alterations in DNA methylation<sup>41</sup>. The principal site of organ damage is the liver, leading to hepatitis, hepatic adenomas and hepatocellular carcinomas in hamsters and other rodents<sup>42,43</sup>. It leads to lung as well as liver tumors in mice with repeated oral doses<sup>39</sup>.

*Limitations during other illnesses or in patients with specific organ dysfunction:* Data on mice, rats and hamsters suggests using extreme caution when giving HS to patients with hepatic dysfunction or in those who use alcohol excessively<sup>44</sup>.

*Interactions with other dietary supplements or pharmaceuticals:* Because HS is a mild monoamine oxidase inhibitor, people using it should avoid foods that are rich in tyramine such as aged cheeses and red wine; Dr. Gold also suggests that patients using HS refrain from using benzodiazepines and barbiturates<sup>34</sup>.

*Safety during pregnancy and/or childhood:* There are no data on safety or toxicity in pregnancy, lactation of childhood.

## ***Typical dosages***

*Provision of dosage information does NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used.*

*Doses are given for single agent use and must be adjusted when using remedies in combinations.*

*Doses may also vary according to the type and severity of the condition treated and individual patient conditions.*

*Typical adult doses of hydrazine sulfate: 60 mg by mouth three to four times daily (TID - QID) for one to three months. It can also be given parenterally as a 0.4 percent solution (15 ml = 60 mg).*

*Pediatric dosages: Unknown*

*Dosages used in combinations: Unknown*

*Brand name: In Europe: Sehydrin.*

*Availability: HS is available in the US through the Investigational New Drug (IND) program of the Food and Drug Administration (FDA). HS is available in Canada through the Health Protection Branch of Health Canada. Additional information is available from Dr. Gold at the Syracuse Center Research Institute, 600 E Genessee St., Syracuse, NY 13202 or at <http://www.ngen.com/hs-cancer>.*

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