

A. INGREDIENT NAME:

DIMERCAPTO-1-PROPANESULFONIC (DMPS)

B. Chemical Name:

DL-2, 3-Dimercapto-1-Propanesulfonic

C. Common Name:

DMPS, Unithiol, Dimaval, Mercuval

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Limit-Min/Max)</i>	<i>(Results)</i>
Assay: (Iodometric)	95%	98.2%

E. Information about how the ingredient is supplied:

Fine, white, crystalline powder, odorless

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Aposhian, H.V. DMSA and DMPS— water soluble antidotes for heavy metal poisoning. *Annual Review of Pharmacology and Toxicology*, 1983; 23: 193-215.

Aposhian, H. V., Maiorino, R. M., and Gonzalez-Ramirez, D. Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology*. 1995; 97(1-3): 23-28.

Chisolm, J. J. BAL, EDTA, DMSA, and DMPS in the treatment of lead poisoning in children. *Clinical Toxicology*, 1992; 30(4): 493-504.

Torr-Alanis, O., Garza-Ocanas, L., and Pineyro-Lopez, A. Evaluation of Urinary Mercury Excretion After Administration of 2,3-Dimercapto-1-propane Sulfonic Acid to Occupationally Exposed Men. *Cinical Toxicology*, 1995; 33(6): 717-720.

Aposhian, H. V., Maiorino, R. M., and Rivera, , M. Human Studies with the Chelating Agents, DMPS and DMSA. *Clinical Toxicology*, 1992; 30(4): 505-528.

Clarkson, T. W., magos, L., and Cox, C. Tests of Efficacy of Antidotes for Removl of Methylmercury in Human Poisoning during the Iraq Outbreak. *The Journal of Pharmacology and Experimental Therapeutics*. 1981; 218: 74-83.

Reynolds, J. E. *Martindale - The extra Pharmacopeia* (31st ed.). London, UK: the Royal Pharmaceutical Society. 1996. 997.

Chisolm, J. J. and Thomas D. J. Use of 2,3-dimercaptopropane-1-Sulfonate in Treatment of Lead Poisoning inChildren. *The Journal of pharmacology and Experimental therapeutics*, 1985; 235(3): 665-669.

Maiorino, R. M., Gonzalez-Ramirez, D., and Zuniga-Charles, M. Sodium 2, 3-Dimercaptopropane-1-Sulfonate Challenge Test for Mercury in Humans. III. Urinary Mercury after Exposure to Mercurous Chloride. *The Journal of Pharmacology and Experimental therapeutics*, 1996; 277(2): 938-944.

Moore, D. F., O'Callaghan, C. A., and Berlyne, G. Acute arsenic poisoning: absence of polyneuropathy after treatment with 2, 3-dimercaptopropanesulphonate (DMPS). *Journal of Neurology, Neurosurgery, and Psychiatry*, 1994; 57: 1133-1135.

Hurlbut, K. M., Maiorino, R. M., and Mayersohn, M. Determination and Metabolism of Dithiol Chelating Agents XVI: Pharmacokinetics of 2,3-Dimercapto-1-Propanesulfonate ater Intravenous Administration to Human Volunteers. *The Journal of Pharmacology and Experimental Therapeutics*. 1994; 268(2): 662-668.

Maiorino, R. M., Xu, Z., and Aposhian, H. V. Determination and Metaboliosm of Dithiol Chelating Agents. XVII. In Humans, Sodium 2,3-Dimercapto-1-Propanesulfonate is Bound to Plasma Albumin Via Mixed Disulfide Formation and is Found in the Urine as Cyclic Polymeric Disulfides. *The Journal of Pharmacology and Experimental Therapeutics*, 1996: 277(1): 375-384.

Aposhian, H. V., Mershon, M. M., and Brinkley, F. B. Anti-lewisite activity anx stability of meso-dimercaptosuccinic acid and 2,3-dimercapto-1-propanesulfonic acid. *Life Sciences*, 1982; 31(19): 2149-2156.

Aposhian, H. V. Biological Chelation: 2,3-dimercapto-propanesulfonic acid and meso-deimercaptosuccinic acid. *Adv Enzyme Regul*, 1982;20: 301-319.

H. Information about dosage forms used:

Capsules

I. Information about strength:

200-400mg

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 230-235°

Stable

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-2205
56203

Page 1

Date: 02/02/98

PRODUCT: DL-2,3-DIMERCAPTO-1-PROPANESULFONIC ACID SOD -

CATALOG NO: YY110 **
LOT NO: NA0487
CUSTOMER NO: PRO055

DESCRIPTION	LIMIT		RESULT
	MIN.	MAX.	
<u>ASSAY (IODOMETRIC)</u>	95 %	-	<u>98.2 %</u> D

APPROVED BY:

Lilian D. Casabar
LILIAN D. CASABAR

2/98



QUALITY CONTROL REPORT

A CHEMICAL NAME.: DIMERCAPTO-1-PROPANESULFONIC

MANUFACTURE LOT NO.: NA0487

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

E FINE, WHITE, CRYSTALLINE POWDER; ODORLESS.

2) SOLUBILITY.:

FREELY SOLUBLE IN WATER; SLIGHTLY SOLUBLE IN ALCOHOL AND IN METHANOL.

3) MELTING POINT.:

MELTS AT ABOUT 230-235 DEGREE.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

PASSES.: _____

FAILS.: _____

COMMENTS.: FULL NAME.: DIMERCAPTO-1-PROPANESULFONIC ACID SODIUM SALT 2,3.

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____



Use your web browser's "Back" key to return to previous topic.

MATERIAL SAFETY DATA SHEET

DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt, Monohydrate 95%
02225

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt, Monohydrate B

Synonyms:

DMP5

Company Identification: Acros Organics N.V.
One Reagent Lane
Fairlawn, NJ 07410

For information in North America, call: 800-ACROS-01

For emergencies in the US, call CHEMTREC: 800-424-9300

For emergencies in the US, call CHEMTREC: 800-424-9300

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
4076-02-2	DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt Monohydrate	95%	223-796-3

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: white.

Caution! Air sensitive. The toxicological properties of this material have not been fully investigated.

Target Organs: None known.

Potential Health Effects

Eye:

No information regarding eye irritation and other potential effects was found.

Skin:

No information regarding skin irritation and other potential effects was found.

Ingestion:

The toxicological properties of this substance have not been fully investigated.

Inhalation:

The toxicological properties of this substance have not been fully investigated. Inhalation of dust may cause respiratory tract

irritation.
 Chronic:
 Not available.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:

Flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.

Skin:

Get medical aid immediately. Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:

If victim is conscious and alert, give 2-4 cupfuls of milk or water. Never give anything by mouth to an unconscious person. Get medical aid immediately.

Inhalation:

Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Notes to Physician:

Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:

As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear.

Extinguishing Media:

Use agent most appropriate to extinguish fire.

Autoignition Temperature: Not available.

Flash Point: Not available.

NFPA Rating: Not published.

Explosion Limits, Lower: Not available.

Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:

Sweep up or absorb material, then place into a suitable clean, dry, closed container for disposal. Avoid generating dusty conditions.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:

Wash thoroughly after handling. Use only in a well ventilated area. Minimize dust generation and accumulation. Avoid contact with eyes, skin, and clothing. Avoid ingestion and inhalation.

Storage:

Store in a cool, dry place. Keep container closed when not in use.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:

Use adequate ventilation to keep airborne concentrations low.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
DI-2,3-Dimercapto-1	none listed	none listed	none listed
-Propanesulfonic Ac			
id, Sodium Salt Mon			
ohydrate			

OSHA Vacated PELs:

DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt Monohydrate:
No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:

Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:

Wear appropriate protective gloves to prevent skin exposure.

Clothing:

Wear appropriate protective clothing to prevent skin exposure.

Respirators:

Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State: Solid
Appearance: white
Odor: None reported.
pH: 5.0 0.5
Vapor Pressure: Not available.
Vapor Density: Not available.
Evaporation Rate: Not available.
Viscosity: Not available.
Boiling Point: @ 760.00mm Hg
Freezing/Melting Point: 229 deg C
Decomposition Temperature: Not available.
Solubility: Not available.
Specific Gravity/Density: Not available.
Molecular Formula: C3H7O3S3Na.H2O
Molecular Weight: 228.28

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:

Stable under normal temperatures and pressures.

Conditions to Avoid:

Not available.

Incompatibilities with Other Materials:

Strong oxidizing agents.

Hazardous Decomposition Products:

Carbon monoxide, oxides of sulfur, carbon dioxide, sodium oxide.

Hazardous Polymerization: Has not been reported.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:

CAS# 4076-02-2: TZ6420000

LD50/LC50:

Not available.

Carcinogenicity:

DI-2,3-Dimercapto-1-Propanesulfonic Acid, Sodium Salt Monohydrate -
Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

Epidemiology:

No data available.

Teratogenicity:

No data available.

Reproductive Effects:

No data available.

Neurotoxicity:

No data available.

Mutagenicity:

No data available.

Other Studies:

No data available.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
Not available.
Environmental Fate:
Not available.
Physical/Chemical:
Not available.
Other:
Not available.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: Not listed.
RCRA U-Series: Not listed.
Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
No information available
IMO
Not regulated as a hazardous material.
IATA
Not regulated as a hazardous material.
RID/ADR
Not regulated as a hazardous material.
Canadian TDG
No information available.

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA

CAS# 4076-02-2 is not listed on the TSCA inventory.
It is for research and development use only.
Health & Safety Reporting List
None of the chemicals are on the Health & Safety Reporting List.
Chemical Test Rules
None of the chemicals in this product are under a Chemical Test Rule.
Section 12b
None of the chemicals are listed under TSCA Section 12b.
TSCA Significant New Use Rule
None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)
None of the chemicals in this material have an RQ.
Section 302 (TPQ)
None of the chemicals in this product have a TPQ.
Section 313
No chemicals are reportable under Section 313.

Clean Air Act:

This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depleters.
This material does not contain any Class 2 Ozone depleters.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

Not present on state lists from CA, PA, MN, MA, FL, or NJ.

California No Significant Risk Level:

None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: Not available.

Risk Phrases:

Safety Phrases:

S 24/25 Avoid contact with skin and eyes.

WGK (Water Danger/Protection)

CAS# 4076-02-2:

Canada

None of the chemicals in this product are listed on the DSL/NDSL list.

WHMIS: Not available.

CAS# 4076-02-2 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 3/07/1992 Revision #3 Date: 9/11/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

[Back](#) to product information.

relatively non-toxic thiocyanate, and thus the detoxification of cyanide.

The dosage regimen in adults is 300 mg of succimer (10 mL of a 3% solution) administered intravenously over 3 minutes followed by sodium thiosulphate (50 mL of a 25% solution or 25 mL of a 50% solution) administered intravenously over a period of about 10 minutes. A dosage regimen in children is 0.15 to 0.25 g per kg body-weight of a 3% solution of succimer (approximately 4.5 to 10.0 mg per kg) followed by 1.65 mL per kg of a 25% solution of sodium thiosulphate (41.25 mg per kg). The methaemoglobin concentration should not exceed 30 to 40% and if symptoms of cyanide toxicity recur, it has been suggested that the injections of nitrite and thiosulphate may be repeated after 30 minutes at half the doses.

Succimer thiosulphate is used as an isotonic 4% solution in the management of extravasation of mustine. It has also been tried in the management of extravasation of some other antineoplastic agents (although not a contentious area, see p.516).

Succimer thiosulphate has antifungal properties and is used topically in the treatment of pityriasis versicolor; the usual treatment of this infection is described on p.397. Sodium thiosulphate and magnesium thiosulphate are included in mixed preparations for a variety of disorders.

The acceptable daily intake of sodium thiosulphate as a nutrient is 700 µg per kg body-weight.

WHO. Evaluation of certain food additives and contaminants—twenty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 631 1978.

WHO. Evaluation of certain food additives and contaminants—twenty-seventh report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 696 1983.

The incidence of sodium thiosulphate given by intravenous infusion in reducing the incidence of nephrotoxicity associated with cisplatin, see under Adverse Effects in p.552.

Bromate poisoning. Sodium thiosulphate has been administered in the treatment of bromate poisoning^{1,2} although its efficacy is unclear.³ Sodium thiosulphate is thought to reduce bromate to the less toxic bromide ion, but experimental evidence is lacking.³ However, the high morbidity associated with bromate poisoning may justify the use of this relatively innocuous compound in some clinical circumstances.⁴

1. *et al.* Bromate poisoning from ingestion of professional-grade neutralizer. *Clin Pharm* 1988; 7: 66-70.

2. *et al.* Bromate poisoning. *J Pediatr* 1989; 114: 20-22.

3. NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; 7: 570, 572.

4. CE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; 7: 572.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

1. Succimer Thiosulphate Injection;
2. Sodium Thiosulfate Injection.

Proprietary Preparations

1. Succimer; Ger.: S-hydriol†.

Ingredient preparations. Aust.: Schwefelbad Dr Klopfer; Itc: Canad.: Adasept; Fr.: Artérise; Désintex; Désintex; Rhino-Sulfuryl; Sulfo-Thiorine Pantothénique†; Ger.: Corti Jaikal; Jaikal; Jodcalcium-POS†; Phera-Sulfat-Dr. Klopfer N; Ital.: Istaglobina†; Salicilato Atro Gamma; Zeta-Bat; S.Afr.: Tripac-Cyano; Spain: Artro Gamma Atro Gamma Vit B1†; Artrochemit†; Nacient Sulf†; Yodo-Sulf†; Switz.: Blephamide; Sébo Lotion; Sulfo-Balmiral†; USA: Cyanide Antidote Package; Komed†; Tinver.

Succimer (1058-k)

(BAN, USAN, rINN).

USA: DMSA, meso-2,3-Dimercaptosuccinic acid; (R',S')-2,3-Dimercapto-butanedioic acid.

$C_4H_8O_7S_2 = 182.2$.

304-55-2.

† denotes a preparation no longer actively marketed

Adverse Effects and Precautions

Succimer may cause gastro-intestinal disorders, skin rashes, increases in serum transaminase, flu-like symptoms, drowsiness, and dizziness. Succimer should be used with caution in patients with impaired renal function or a history of hepatic disease.

Pharmacokinetics

Following oral administration succimer is rapidly but incompletely absorbed. It undergoes rapid and extensive metabolism and is excreted mainly in the urine with small amounts excreted in the faeces and via the lungs.

References

1. Dart RC, *et al.* Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults. *J Pediatr* 1994; 125: 309-16.

Uses and Administration

Succimer is a chelating agent structurally related to dimercaprol (see p.980). It forms water-soluble chelates with heavy metals and is used in the treatment of acute poisoning with lead, arsenic, or mercury.

Succimer may also be used in the management of cystinuria. Succimer, labelled with a radionuclide, is used in nuclear medicine.

In the treatment of lead poisoning, succimer is given by mouth in a suggested dose of 10 mg per kg body-weight or 350 mg per m² body-surface area every 8 hours for 5 days then every 12 hours for an additional 14 days. The course of treatment may be repeated if necessary, usually after an interval of not less than 2 weeks. The management of lead poisoning, including the use of succimer, is discussed under Lead. Treatment of Adverse Effects, p.1720.

Reviews

1. Anonymous. Succimer—an oral drug for lead poisoning. *Med Lett Drugs Ther* 1991; 33: 78.
2. Mann KV, Travers JD. Succimer, an oral lead chelator. *Clin Pharm* 1991; 10: 914-22.

Extracorporeal administration. Extracorporeal infusion of succimer into the arterial blood line during haemodialysis, a procedure known as extracorporeal regional complexing haemodialysis, produced a substantial clearance of mercury in an anuric patient following intoxication with inorganic mercury.¹ Clearance was approximately ten times greater than that achieved with haemodialysis following intramuscular administration of dimercaprol.

1. Kostyniak PJ, *et al.* Extracorporeal regional complexing haemodialysis treatment of acute inorganic mercury intoxication. *Hum Toxicol* 1990; 9: 137-41.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

USA: Chemet.

Trientine Dihydrochloride (13377-a)

Trientine Dihydrochloride (BAN, rNNM).

MK-0681; Trien Hydrochloride; Trientine Hydrochloride (USAN); Triethylenetetramine Dihydrochloride. 2,2'-Ethylene-di-iminobis(ethylamine) dihydrochloride; N,N'-bis(2-Aminoethyl)-1,2-ethanediamine dihydrochloride.

$C_8H_{18}N_4 \cdot 2HCl = 219.2$.

CAS — 112-24-3 (trientine); 38260-01-4 (trientine dihydrochloride).

Pharmacopoeias. in US.

A white to pale yellow crystalline powder. Freely soluble in water; soluble in methyl alcohol; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 1% solution in water has a pH of 7.0 to 8.5. Store under an inert gas in airtight containers at 2° to 8°. Protect from light.

Adverse Effects and Precautions

Trientine dihydrochloride may cause iron deficiency. If iron supplements are given an interval of at least 2 hours between the administration of a dose of trientine and iron has been recommended. Recurrence of symptoms of systemic lupus erythematosus has been reported in a patient who had previously reacted to penicillamine.

Uses and Administration

Trientine dihydrochloride is a copper chelating agent used in a similar way to penicillamine in the treatment of Wilson's disease. It tends to be used in patients intolerant to penicillamine. For a discussion of the management of Wilson's disease see p.992.

Trientine dihydrochloride is administered by mouth, preferably on an empty stomach. The usual initial dose is 750 mg to 1250 mg daily in 2 to 4 divided doses increasing to a maximum of 2 g daily if required. In children, the usual initial dose is 500 to 750 mg daily increasing to a maximum of 1.5 g daily if required.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Trientine Hydrochloride Capsules.

Proprietary Preparations

USA: Syprine.

Unithiol (1059-a)

DMPS; Unithiol; Sodium 2,3-dimercaptopropanesulphonate.

$C_3H_7NaO_3S_3 = 210.3$.

CAS — 4076-02-2.

Unithiol is a chelating agent structurally related to dimercaprol (see p.980). It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, inorganic and organic mercury compounds, and chromium. It may be less effective in cadmium poisoning.

Unithiol is given by mouth in doses of 100 mg three times daily. It has also been administered parenterally.

Reviews

1. Aposhian HV. DMSA and DMPS—water soluble antidotes for heavy metal poisoning. *Ann Rev Pharmacol Toxicol* 1983; 23: 193-215.
2. Hruby K, Donner A. 2,3-Dimercapto-1-propanesulphonate in heavy metal poisoning. *Med Toxicol* 1987; 2: 317-23.

Lead poisoning. Unithiol has been tried in twelve children with chronic lead poisoning.¹ It reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma. During treatment the urinary excretion of lead, copper, and zinc was increased.

The usual chelating agents used in the management of lead poisoning are discussed on p.1720.

1. Chisolm JJ, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulphonate in treatment of lead poisoning in children. *J Pharmacol Exp Ther* 1985; 235: 665-9.

Mercury poisoning. Administration of unithiol 100 mg twice daily by mouth for a maximum of 15 days enhanced urinary elimination of mercury in 7 patients with mercury poisoning.¹ The urinary elimination of copper and zinc was also increased in most patients and two developed skin rashes. Unithiol, 50 mg per 10 kg body-weight by intramuscular injection three times a day reducing to 50 mg per 10 kg once a day by the third day of treatment, effectively reduced the half-life of mercury in the blood following poisoning with methylmercury.²

1. Mant TGK. Clinical studies with dimercaptopropane sulphate in mercury poisoning. *Hum Toxicol* 1985; 4: 346.
2. Clarkson TW, *et al.* Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J Pharmacol Exp Ther* 1981; 218: 74-83.

Wilson's disease. Unithiol 200 mg twice daily¹ was used successfully to maintain cupriuresis in a 13-year-old boy with Wilson's disease after he developed systemic lupus during treatment with penicillamine and with trientine dihydrochloride, which are two of the usual agents used in Wilson's disease (see p.992). Unithiol was started in two similar patients¹ but both withdrew from treatment, one because of fever and a fall in leucocyte count following a test dose and the other because of intense nausea and taste impairment.

1. Walshe JM. Unithiol in Wilson's disease. *Br Med J* 1985; 290: 673-4.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Ger.: Dimaval; Mercuvial, C

UNIVERSITY OF HOUSTON
COLLEGE OF PHARMACY
HOUSTON, TEXAS

2, 3-DIMERCAPTO-1-PROPANE SULFONIC ACID (DMPS) IN THE TREATMENT OF HEAVY METAL POISONING

*Hong (Rose) Ton Nguyen, Pharm. D. Candidate
University of Houston
College of Pharmacy
Houston, Texas*

February 17 through March 28, 2007

2, 3-DIMERCAPTO-1-PROPANE SULFONIC ACID (DMPS) IN THE TREATMENT OF HEAVY METAL POISONING

Introduction

The use of chelating agents, such as BAL (British Anti-Lewisite), calcium disodium EDTA, and penicillamine in the treatment of human exposure to toxic metals has been well known and accepted (1, 2, 3). However, these chelating agents have limited therapeutic efficacies and undesirable side effects. In the quest for therapeutically more potent and less toxic metal-binding agents to use in the treatment of heavy metal poisoning, scientists have found that the sodium salt of 2, 3-dimercapto-1-propanesulfonic acid (DMPS) is an example of such a compound (2, 4). It is a water-soluble chemical analog of dimercaprol (BAL) but is less toxic. It is administered parenterally and is also effective when given orally. It has been used as an official drug in the Soviet Union since 1958 as Unithiol®. DMPS has been approved by the German Food and Drug Administration (FDA) and is manufactured by Heyl & Co. in Berlin, Germany as Dimaval®. However, it is a relatively new antidote, especially to this country; it is being used in the United States as an investigational drug (2).

Chemical Properties

Structurally, DMPS is related to BAL (Figure 1) (1, 2, 3). It is a sulfonic acid salt with two free sulfhydryl groups (SH-) which form complexes with heavy metals, such as mercury

(Hg), cadmium (Cd), arsenic (As), lead (Pb), copper (Cu), silver (Ag), tin (Sn), and others. It is soluble in water and can be administered parenterally as well as orally. DMPS has a distinct odor; thus, it is recommended to administer the drug in ice cold orange juice or in ice cold apple sauce (3). In addition, stability studies on DMPS are currently not available, but it is considered to be very stable and not readily oxidized during pre-use storage.

Therapeutic Use

As mentioned earlier, DMPS is used in the treatment of poisoning in humans by heavy metals including mercury, arsenic, and lead (Table 1) (2, 6, 8, 9, 10). It is registered with the German FDA for the treatment of mercury poisoning and is in fact sold in Germany without the need of a prescription (2). It has also been used as a mercury challenge or diagnostic test for mercury exposure; it has been found as the ideal agent to detoxify patients that have suffered from mercury toxicity from dental amalgam fillings after the fillings have been removed (1, 5, 6). Moreover, DMPS has been reported to be useful in Wilson's disease in which tissue levels of copper are high. It is given by mouth as a single dose of 300 mg or 100 mg three times daily for as long as 15 days. In the treatment of lead poisoning in children an oral dose of 200 mg to 400 mg of DMPS per meter squared body surface area per day was used effectively without observable adverse drug reactions (8). When given parenterally, 5 mg per kg body weight three times a day was the recommended dose(7).

H
I
J

Pharmacokinetic Studies

DMPS has been extensively used in humans both in the Soviet Union and in Germany, and pharmacokinetic data after intravenous (IV) and oral (PO) administration of this drug are widely available (1, 2, 11, 12). Studies have shown that DMPS is distributed both extracellularly and to a smaller extent intracellularly (5, 11). Scientists made an assumption that if the drug appeared in the bile then it must have entered liver cells first, and experiments done in rats proved that DMPS does enter the liver cells in small amounts (5). H
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In the plasma, DMPS is found to be about 62.5% bound by protein, mainly albumin, via a disulfide linkage (5, 11, 12). This was elucidated by treating the isolated DMPS-albumin complex from the urine with dithiothreitol (DTT) to give back DMPS, the parent compound. The DMPS-albumin disulfide complex is quite stable and may prolong the heavy metal mobilizing activity of DMPS. As a matter of fact, the half-life of the parent compound was 1.8 hours; whereas, that of altered DMPS was 20 hours.

DMPS is metabolized rapidly and is eliminated in the kidney and bile (4, 5, 11, 12). Hurlbut, *et. al.* (1994) demonstrated that only about 12% or 9%, respectively, of the DMPS concentration detected in the urine is presented as the parent drug after fifteen minutes of IV or PO administration of DMPS, suggesting that the majority of the DMPS in the urine were the metabolites or the oxidized forms of the drug (12). In humans, DMPS is biotransformed or oxidized to acyclic polymeric disulfides (which constitute only 0.5% of the total DMPS disulfides) in the liver and cyclic polymeric disulfides (97% of the total DMPS disulfides) in the bile (Figure 2) (2, 5, 12). The amount of altered or unaltered DMPS was determined

using an assay that employed the chemical known as bromobimane to react with the thiols (Figure 3) (5, 12). Neither bromobimane nor DMPS has a fluorescence, but bromobimane would react with DMPS to form a highly fluorescent bimane derivative. The resulting compound is then analyzed using the technique of HPLC (High-Performance Liquid Chromatography) to detect unaltered molecules. The value of the altered or biotransformed molecules of the drug is then determined by subtracting the value of experimentally determined unaltered forms from the value of experimentally determined total DMPS (5).

Nevertheless, the disulfide group and certainly the sulfonic group are very poor chelators, especially of mercury or lead (12). The two sulfhydryl groups of DMPS are necessary for chelation. DMPS disulfides appear to be transported and reduced to DMPS within the renal tubules in the kidney where chelation of mercury by DMPS increases mercury excretion in the urine.

Oral DMPS appears to be less effective; oral bioavailability of DMPS is about 60% (11). The half-life found for total DMPS in a study after IV administration was approximately 20 hours, which was considerably longer than the half-life of 9.5 hours found for total DMPS after oral administration to humans (11). These values may represent differences in the metabolites produced after oral and IV administration. Other pharmacokinetic parameters of the drug include an elimination half-life of 43 minutes, a volume of distribution (Vd) of 160 ml/kg, and a clearance (CL) of 2.6 ml/min/kg (1, 11).

Toxicities

DMPS is a relatively safe drug and has been used innocuously in Europe for many years (1). In the studies done on DMPS at a dose of 5 mg/kg, some patients developed allergic reactions to the drug. This is usually because the patients have a history of allergies. No anaphylactic shock was seen. Other common side effects experienced by some patients were mild and include nausea, weakness, vertigo, and itching skin. No nephrotoxicity was observed. It also exhibited no mutagenic or teratogenic effects (1). When the dosage was increased to 100 mg/kg, the increased effectiveness was noted, but necrotization and ulcerations often occurred at the site of the subcutaneous (SC) or IV injection. However, when injected IV, DMPS should be given over a five minute period since hypotensive effects are possible when it is given parenterally as a bolus (2).

DMPS vs. Other Chelating Agents

In the treatment of heavy metal poisoning, BAL and calcium disodium EDTA are becoming obsolete. Water-soluble chelating agents like DMSA (succimer, Chemet®) and DMPS are therapeutically more potent and less toxic (1, 2, 5). When compared with D-penicillamine and N-acetyl DL-penicillamine, DMPS was the most effective for clearing mercury from the blood (6). It is more advantageous than DMSA since it has been extensively used in the Soviet Union and in Germany, and capsules for oral use as well as parenteral preparations of DMPS are available. DMSA, on the other hand, is only available

orally, thus, pharmacokinetics of DMSA are somewhat limited. Additionally, DMPS does not cause a redistribution of Hg to the brain like calcium disodium EDTA can. DMPS is more specific than calcium disodium EDTA; at diagnostic doses, DMPS would not be expected to increase the urinary excretion of essential trace elements such as copper and zinc. DMPS is able to enter cells to a certain extent and thus is intermediate in its toxicity. Comparatively, DMSA is the least toxic of the dimercapto chelating agents and has the highest LD₅₀ since it does not get into cells (Table 2).

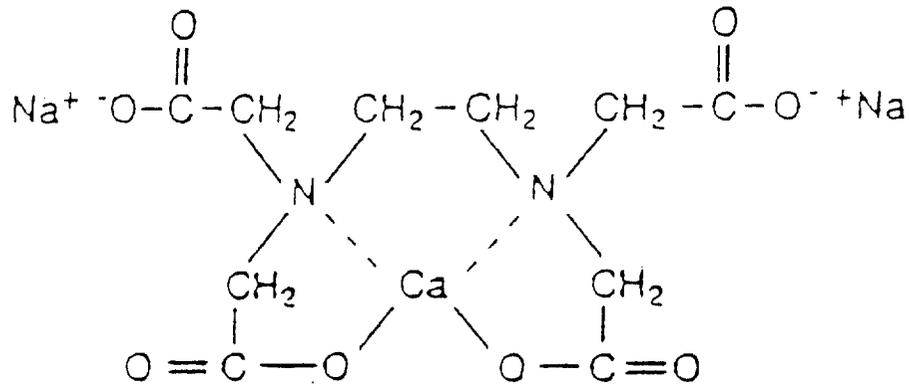
Conclusion

In retrospect, it appears that there is no better chelating agent than DMPS in treating heavy metal poisoning. None of the other chelating agents including DMSA, BAL, penicillamine, or calcium disodium EDTA is as therapeutically diverse and potent in detoxifying patients of heavy metals as DMPS. Other chelating agents are more toxic to use; whereas, DMPS is a relatively safe drug. Thus, in the treatment of heavy metal poisoning 2, 3-dimercapto-1-propane sulfonic acid is the recommended choice.

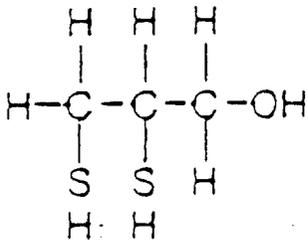
Figure 1

Chemical formulas for chelating agents used for treating heavy metal poisoning of humans

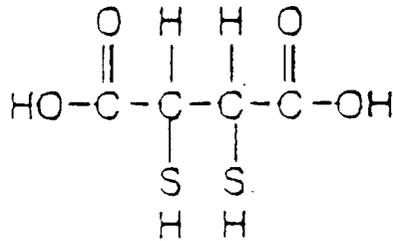
(From Reference #2)



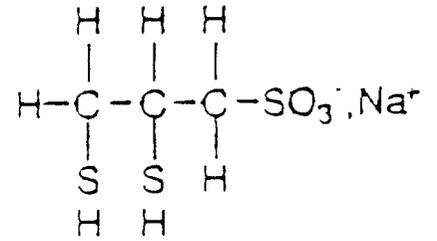
CaNa₂EDTA
(Edetate Calcium Disodium)



Dimercaprol
(British Antilewisite, BAL)



DMSA
(Meso-Dimercapto Succinic Acid)
Succimer



DMPS
(2,3-Dimercapto-1-Propane-
Sulfonic Acid, Na Salt)
Dimaval

Figure 2

Proposed Structures of the human urinary metabolites of DMPS (From Reference # 12)

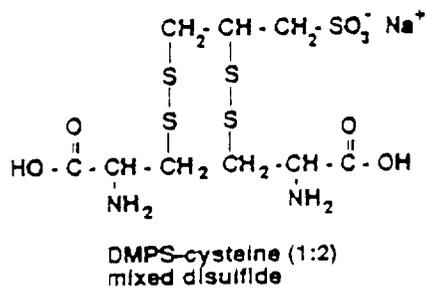
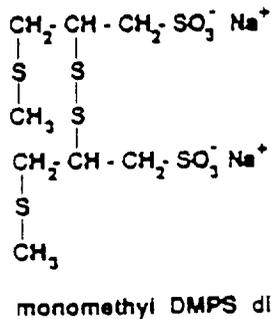
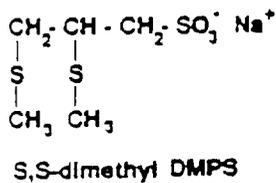
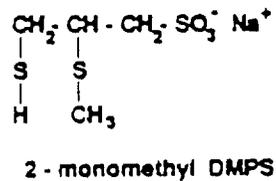
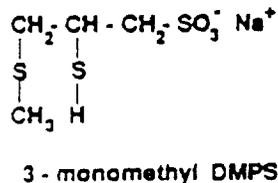
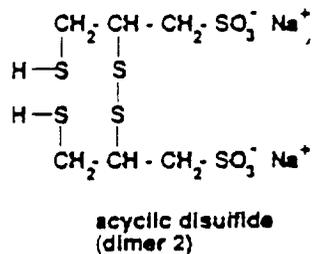
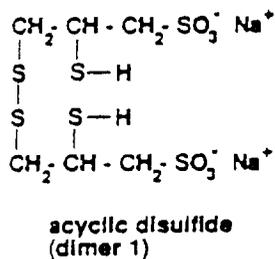
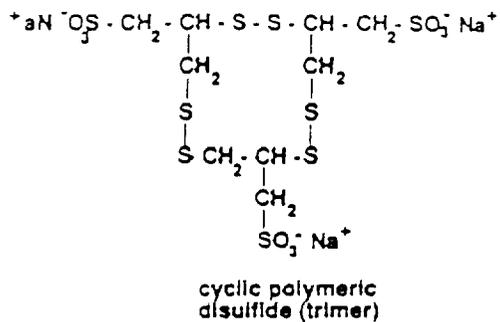
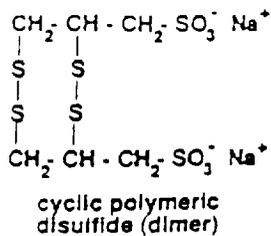


Figure 3

Proposed Reactions of bromobimane with DMPS (From Reference #5)

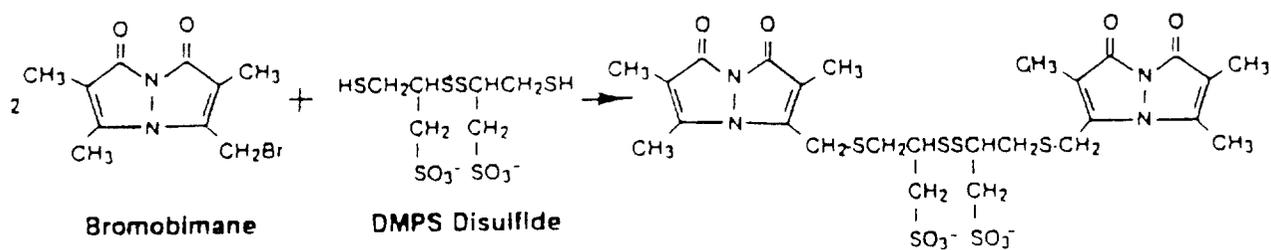
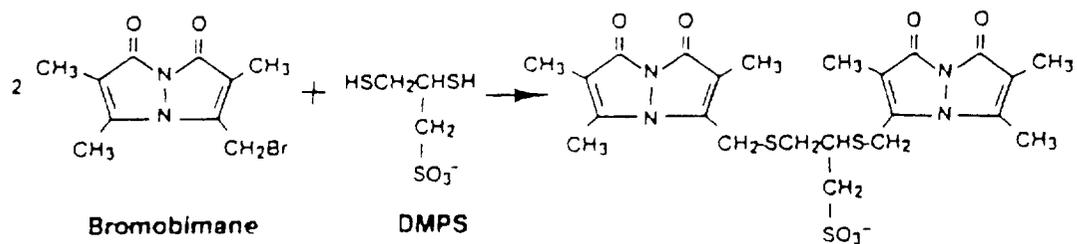


Table 1

Indications and Contraindications of chelating agents in heavy metal poisonings
(From Reference #2)

Metal*	First Choice	Second Choice	Contraindications
Hg metal	DMPS	DMSA	Dimercaprol
Hg inorganic	DMPS	DMSA	Dimercaprol
Hg organic	DMSA, DMPS		Dimercaprol
Pb	DMSA	DMPS	Dimercaprol, EDTA
As	DMPS, DMSA	Dimercaprol	Dimercaprol (?)
Cr	DMPS		
Sb	DMPS		
Transuranics	DTPA		

*Abbreviations: Hg= mercury; Pb= lead, As= arsenic; Cr=chromium; Sb=antimony.

Table 2

*LD₅₀ Determination intraperitoneally in mice (From Reference #5)

Compound	LD ₅₀ (mmol/kg)	95% confidence interval	Number of mice
BAL	1.48	1.11, 1.97	212
DMPA	0.82	0.80, 0.84	172
DMPS	6.53	5.49, 7.71	88
meso-DMSA	13.73	11.36, 15.22	164

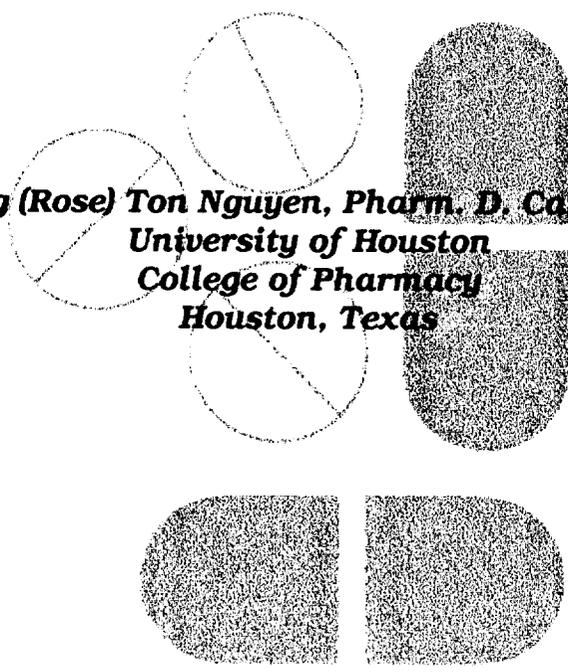
*LD₅₀ = median lethal dose.

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**2, 3-DIMERCAPTO-1-PROPANE SULFONIC ACID (DMPS)
IN THE TREATMENT OF HEAVY METAL POISONING**

A stylized graphic consisting of several pill shapes. On the left, there are two circular pills with diagonal lines. To their right are two vertical oval pills with a stippled texture. Below these is a single horizontal oval pill, also with a stippled texture.

***Hong (Rose) Ton Nguyen, Pharm. D. Candidate
University of Houston
College of Pharmacy
Houston, Texas***

February 17 through March 28, 1997

2, 3-DIMERCAPTO-I-PROPANE SULFONIC ACID (DMPS) IN THE TREATMENT OF HEAVY METAL POISONING

Introduction

The use of chelating agents, such as BAL (British Anti-Lewisite), calcium disodium EDTA, and penicillamine in the treatment of human exposure to toxic metals has been well known and accepted (1, 2, 3). However, these chelating agents have limited therapeutic efficacies and undesirable side effects. In the quest for therapeutically more potent and less toxic metal-binding agents to use in the treatment of heavy metal poisoning, scientists have found that the sodium salt of 2, 3-dimercapto-I-propanesulfonic acid (DMPS) is an example of such a compound (2, 4). It is a water-soluble chemical analog of dimercaprol (BAL) but is less toxic. It is administered parenterally and is also effective when given orally. It has been used as an official drug in the Soviet Union since 1958 as Unithiol®. DMPS has been approved by the German Food and Drug Administration (FDA) and is manufactured by Heyl & Co. in Berlin, Germany as Dimaval®. However, it is a relatively new antidote, especially to this country; it is being used in the United States as an investigational drug (2).

Chemical Properties

Structurally, DMPS is related to BAL (Figure 1) (1, 2, 3). It is a sulfonic acid salt with two free sulfhydryl groups (SH-) which form complexes with heavy metals, such as mercury (Hg), cadmium (Cd), arsenic (As), lead (Pb), copper (Cu), silver (Ag), tin (Sn), and others. It is soluble in water and can be administered parenterally as well as orally. DMPS has a distinct odor; thus, it is recommended to

administer the drug in ice cold orange juice or in ice cold apple sauce (3). In addition, stability studies on DMPS are currently not available, but it is considered to be very stable and not readily oxidized during pre-use storage.

Therapeutic Use

As mentioned earlier, DMPS is used in the treatment of poisoning in humans by heavy metals including mercury, arsenic, and lead (Table I) (2, 6, 8, 9, 10). It is registered with the German FDA for the treatment of mercury poisoning and is in fact sold in Germany without the need of a prescription (2). It has also been used as a mercury challenge or diagnostic test for mercury exposure; it has been found as the ideal agent to detoxify patients that have suffered from mercury toxicity from dental amalgam fillings after the fillings have been removed (1, 5, 6). Moreover, DMPS has been reported to be useful in Wilson's disease in which tissue levels of copper are high. It is given by mouth as a single dose of 300 mg or 100 mg three times daily for as long as 15 days. In the treatment of lead poisoning in children an oral dose of 200 mg to 400 mg of DMPS per meter squared body surface area per day was used effectively without observable adverse drug reactions (8). When given parenterally, 5 mg per kg body weight three times a day was the recommended dose(7).

Pharmacokinetic Studies

DMPS has been extensively used in humans both in the Soviet Union and in Germany, and pharmacokinetic data after intravenous (IV) and oral (PO) administration of this drug are widely available (1, 2, 11, 12). Studies have shown that DMPS is distributed both extracellularly and to a smaller extent

intracellularly (5, 11). Scientists made an assumption that if the drug appeared in the bile then it must have entered liver cells first, and experiments done in rats proved that DMPS does enter the liver cells in small amounts (5).

In the plasma, DMPS is found to be about 62.5% bound by protein, mainly albumin, via a disulfide linkage (5, 11, 12). This was elucidated by treating the isolated DMPS-albumin complex from the urine with dithiothreitol (DTT) to give back DMPS, the parent compound. The DMPS-albumin disulfide complex is quite stable and may prolong the heavy metal mobilizing activity of DMPS. As a matter of fact, the half-life of the parent compound was 1.8 hours; whereas, that of altered DMPS was 20 hours.

DMPS is metabolized rapidly and is eliminated in the kidney and bile (4, 5, 11, 12). Hurlbut, *et al.* (1994) demonstrated that only about 12% or 9%, respectively, of the DMPS concentration detected in the urine is presented as the parent drug after fifteen minutes of IV or PO administration of DMPS, suggesting that the majority of the DMPS in the urine were the metabolites or the oxidized forms of the drug (12). In humans, DMPS is biotransformed or oxidized to acyclic polymeric disulfides (which constitute only 0.5% of the total DMPS disulfides) in the liver and cyclic polymeric disulfides (97% of the total DMPS disulfides) in the bile (Figure 2) (2, 5, 12). The amount of altered or unaltered DMPS was determined using an assay that employed the chemical known as bromobimane to react with the thiols (Figure 3) (5, 12). Neither bromobimane nor DMPS has a fluorescence, but bromobimane would react with DMPS to form a highly fluorescent bimane derivative. The resulting compound is then analyzed using the technique of HPLC (High-Performance Liquid Chromatography) to detect unaltered molecules. The value of the altered or biotransformed molecules of the drug is then determined by subtracting the

pharmacokinetic and pharmacodynamic (PK/PD) data of (IV) and oral (PO) administration of this drug are widely available (1, 2, 11, 12). Studies have shown that DMPS is distributed both extracellularly and to a smaller extent

Nevertheless, the disulfide group and certainly the sulfonic group are very poor chelators, especially of mercury or lead (I2). The two sulfhydryl groups of DMPS are necessary for chelation. DMPS disulfides appear to be transported and reduced to DMPS within the renal tubules in the kidney where chelation of mercury by DMPS increases mercury excretion in the urine.

Oral DMPS appears to be less effective; oral bioavailability of DMPS is about 60% (II). The half-life found for total DMPS in a study after IV administration was approximately 20 hours, which was considerably longer than the half-life of 9.5 hours found for total DMPS after oral administration to humans (II). These values may represent differences in the metabolites produced after oral and IV administration. Other pharmacokinetic parameters of the drug include an elimination half-life of 43 minutes, a volume of distribution (Vd) of 160 ml/kg, and a clearance (CL) of 2.6 ml/min/kg (I, II).

Toxicities

DMPS is a relatively safe drug and has been used innocuously in Europe for many years (I). In the studies done on DMPS at a dose of 5 mg/kg, some patients developed allergic reactions to the drug. This is usually because the patients have a history of allergies. No anaphylactic shock was seen. Other common side effects experienced by some patients were mild and include nausea, weakness, vertigo, and itching skin. No nephrotoxicity was observed. It also exhibited no mutagenic or teratogenic effects (I). When the dosage was increased to 100 mg/kg, the increased effectiveness was noted, but necrotization and ulcerations often occurred at the site of the subcutaneous (SC) or IV injection. However, when injected IV, DMPS should be given over a five minute period since hypotensive effects are possible when it is given

parenterally as a bolus (2).

DMPS vs. Other Chelating Agents

In the treatment of heavy metal poisoning, BAL and calcium disodium EDTA are becoming obsolete. Water-soluble chelating agents like DMSA (succimer, Chemet®) and DMPS are therapeutically more potent and less toxic (1, 2, 5). When compared with D-penicillamine and N-acetyl DL-penicillamine, DMPS was the most effective for clearing mercury from the blood (6). It is more advantageous than DMSA since it has been extensively used in the Soviet Union and in Germany, and capsules for oral use as well as parenteral preparations of DMPS are available. DMSA, on the other hand, is only available orally, thus, pharmacokinetics of DMSA are somewhat limited. Additionally, DMPS does not cause a redistribution of Hg to the brain like calcium disodium EDTA can. DMPS is more specific than calcium disodium EDTA; at diagnostic doses, DMPS would not be expected to increase the urinary excretion of essential trace elements such as copper and zinc. DMPS is able to enter cells to a certain extent and thus is intermediate in its toxicity.

Comparatively, DMSA is the least toxic of the dimercapto chelating agents and has the highest LD₅₀ since it does not get into cells (Table 2).

Conclusion

In retrospect, it appears that there is no better chelating agent than DMPS in treating heavy metal poisoning. None of the other chelating agents including DMSA, BAL, penicillamine, or calcium disodium EDTA is as therapeutically diverse and potent in detoxifying patients of heavy metals as DMPS. Other

chelating agents are more toxic to use; whereas, DMPS is a relatively safe drug. Thus, in the treatment of heavy metal poisoning

2, 3-dimercapto-1-propane sulfonic acid is the recommended choice.

Figure I

Chemical formulas for chelating agents used for treating heavy metal poisoning of humans (From Reference #2)

Figure 2

Proposed Structures of the human urinary metabolites of DMPS (From Reference # 12)

Figure 3

Proposed Reactions of bromobimane with DMPS (From Reference #5)

Table I

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(From Reference #2)

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*Abbreviations: Hg= mercury; Pb= lead; As= arsenic; Cr=chromium; Sb=antimony.

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Database: Medline <1966 to present>

<1>

Unique Identifier

83087787

Authors

Aposhian HV. Mershon MM. Brinkley FB. Hsu CA. Hackley BE.

Title

Anti-lewisite activity and stability of meso-dimercaptosuccinic acid and 2,3-dimercapto-1-propanesulfonic acid.

Source

Life Sciences. 31(19):2149-56, 1982 Nov 8.

Abstract

Meso-dimercaptosuccinic acid (DMSA) and the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) are analogous in chemical structure to dimercaprol (BAL, British Anti-Lewisite). Dimercaprol was among the first therapeutically useful metal chelating agents and was developed originally as an anti-lewisite agent. Either DMSA or DMPS protects rabbits from the lethal systemic action of dichloro(2-chlorovinyl)arsine (29.7 $\mu\text{mol}/\text{kg}$, also known as lewisite. The analogs are active in this respect when given either sc or po. The stability of each of the three dimercapto compounds in distilled H₂O, pH 7.0 at 24 degrees, has been examined for seven days. DMSA retained 82% of its mercapto groups, but no titratable mercapto groups remained in the DMPS or BAL solutions. At pH 5.0, however, there was no striking difference in the stability of the three dimercapto compounds (78-87%) over a seven day period. DMSA and DMPS warrant further investigation as water soluble metal binding agents in both in vivo and in vitro experiments.

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please order



TITLE: Biological chelation: 2,3-dimercapto-propanesulfonic acid and meso-dimercaptosuccinic acid.

AUTHOR: Aposhian HV

SOURCE: Adv Enzyme Regul 1982;20:301-19

NLM CIT. ID: 82280847

ABSTRACT: **Water soluble analogs of British Anti-Lewisite that are active orally and less toxic than BAL are now available. These agents are 2,3-dimercapto-1-propanesulfonic acid and meso-dimercaptosuccinic acid. Evidence for their effectiveness in preventing the lethal effects of sodium arsenite in mice and lewisite in rabbits is presented. These analogs can be expected to replace BAL in the treatment of heavy metal poisoning.**

MAIN MESH SUBJECTS: Chelating Agents/*PHARMACOLOGY
Dimercaprol/*ANALOGS & DERIVATIVES/PHARMACOLOGY
Succimer/*PHARMACOLOGY
Sulfhydryl Compounds/*PHARMACOLOGY
Unithiol/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS: Animal
Arsenic/POISONING
Cadmium Poisoning
Lethal Dose 50
Male
Mice
Penicillamine/ANALOGS & DERIVATIVES/PHARMACOLOGY
Support, Non-U.S. Gov't

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Chelating Agents)
0 (Sulfhydryl Compounds)
13768-07-5 (sodium arsenite)
304-55-2 (Succimer)
4076-02-2 (Unithiol)
52-67-5 (Penicillamine)
59-52-9 (Dimercaprol)
59-53-0 (N-acetylpenicillamine)
7440-38-2 (Arsenic)

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**ANTI-LEWISITE ACTIVITY AND STABILITY OF MESO-DIMERCAPTOSUCCINIC
ACID AND 2,3-DIMERCAPTO-1-PROPANESULFONIC ACID**

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(Received in final form August 9, 1982)

Summary

Meso-dimercaptosuccinic acid (DMSA) and the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) are analogous in chemical structure to dimercaprol (BAL, British Anti-Lewisite). Dimercaprol was among the first therapeutically useful metal chelating agents and was developed originally as an anti-lewisite agent. Either DMSA or DMPS protects rabbits from the lethal systemic action of dichloro(2-chlorovinyl)arsine (29.7 μ moles/kg, also known as lewisite. The analogs are active in this respect when given either sc or po. The stability of each of the three dimercapto compounds in distilled H₂O, pH 7.0 at 24°, has been examined for seven days. DMSA retained 82% of its mercapto groups, but no titratable mercapto groups remained in the DMPS or BAL solutions. At pH 5.0, however, there was no striking difference in the stability of the three dimercapto compounds (78-87%) over a seven day period. DMSA and DMPS warrant further investigation as water soluble metal binding agents in both in vivo and in vitro experiments.

British Anti-Lewisite (BAL, dimercaprol) was developed in the 1940's as an antidote to dichloro-(2-chlorovinyl)-arsine, commonly called lewisite (1,2). The lethal action of lewisite is believed to be the result of its combining with one or more sulfhydryl groups and thus inactivating essential sulfhydryl-containing enzymes (3). It is the arsenic in the lewisite molecule that reacts with sulfhydryl moieties.

At the time of its introduction into clinical medicine, BAL was considered by many to be the long sought, universal antidote for heavy metal poisoning. In subsequent years, however, less toxic and more specific metal binding agents have been sought and investigated. Some have met the criteria and standards necessary for clinical use. Others have not. For example, BAL glucoside was introduced (4) as a result of a search for water soluble and less toxic analogs of BAL. Although it was found to be less toxic than BAL for iv use, (probably because of its low lipoid solubility), it did not become established as a clinical agent because it is unstable chemically. Other compounds, which are less analogous in chemical structure, have replaced BAL for some of its more specific therapeutic uses. For example, D-penicillamine is used to mobilize and increase the excretion of copper in patients with Wilson's Disease (5). Its N-acetyl derivative is effective as a mercury antidote (6,7). BAL has remained, however, the drug of choice in the U.S. for the treatment of arsenic poisoning.

Meso-dimercaptosuccinic acid (DMSA) (8) and the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) (9) are promising replacements for BAL. These compounds are very similar in chemical structure to BAL and are sometimes referred to as water soluble and/or orally-effective analogs of BAL. To our knowledge, however, the anti-lewisite activity of these two important chemical analogs has not been determined. Neither are any published data available concerning the stability of aqueous solutions of these dimercapto compounds. Evidence for the anti-lewisite activity and stability of DMPS and DMSA are presented in this paper.

Materials and Methods

Male New Zealand white stock rabbits weighing 2.5-3.5 kg were purchased from Dutchland Laboratories Inc., Denver, PA and Davidson Mill Farm, Jonesburg, NJ and caged individually. Food (Purina Rabbit Chow Brand 5322) and water were available *ad libitum* except in the case of those animals who received therapy orally. Animals receiving therapy *po* were fasted from 16 hrs prior to the first administration to 1 hr after the last administration on day one. On days two and three, animals were fasted from 1 hr prior to the morning administration to 1 hr after the evening administration, approximately 7 hours.

When dithiol therapy was given *sc*, the animals were anesthetized fifteen minutes before lewisite administration by administering *im* 0.50 ml of anesthetic solution per kg. The animals were anesthetized to reduce the pain expected to be caused by lewisite. Subsequently, it was observed that neither pain nor discomfort was apparent. Thus, anesthesia was not used in the experiments when dithiols were given *po*. The anesthetic solution was prepared by mixing 5 parts Ketamine HCl (100 mg/ml) and 1 part of Xylazine (100 mg/ml).

A 5 ml Gilson Pipetman was used to give the dithiols by mouth. The rabbit was placed in a short restraining box. The box was placed on its end so that the rabbit was in a vertical position with its head at the top. The Pipetman was filled with the desired volume of the drug solution. The plastic tip was gently inserted between the lips at one corner of the mouth and the liquid delivered slowly into the back of the rabbit's mouth. This method did not appear to cause any trauma or injury. It was easier and faster to perform than the use of polyethylene stomach tubes.

NaDMPS was a gift of Heyl and Co., Berlin. Since each molecule has a molecule of H_2O associated with it, a molecular weight of 228.2 was used in calculations. DMSA was a gift of Johnson and Johnson, Skillman, N.J. Both compounds were pharmaceutical grade purity. DMPS and DMSA were titrated with iodine in order to measure purity and mercapto content. By this criterion, each preparation was judged to be greater than 99% pure. The compounds when given by mouth were dissolved in water. In order to dissolve DMSA, the aqueous suspension was adjusted to pH 5.5 with NaOH. When given *sc*, the solutions were prepared the same way except that the compounds were dissolved in 0.9% NaCl-5% $NaHCO_3$. Unless otherwise stated, the concentrations of DMPS or DMSA were such that the rabbit received 1.0 ml of solution per kg of body weight, per administration. Dimercaprol Injection, USP (BAL in Oil Ampules) was a gift of Hynson, Wescott & Dunning, Baltimore, MD.

Lewisite was 97-99.6% pure as judged by NMR-spectroscopy as well as by iodine titration. Analysis by the former method also indicated that the forms of lewisite that were present were *trans* (97.7%), *cis* (1.7%) and dimers (0.5%). Lewisite is a hazardous material with which to work since it is a potent vesicant. All handling of lewisite was done in an extremely well

TABLE I

The Anti-Lewisite Activity of Meso-Dimercaptosuccinic Acid and 2,3,-Dimercapto-1-Propanesulfonate when given sc to rabbits

Group	$\mu\text{mols/kg}$	survive/start ^a	% survival
1	LEW ^b + -----	1/18	6
2	LEW + 75.0 DMSA ^c	12/12	100
3	LEW + 37.5 DMSA	6/6	100
4	LEW + 20.0 DMSA	6/6	100
5	LEW + 10.0 DMSA	1/6	17

6	LEW + 75.0 DMPS ^c	10/12	83
7	LEW + 37.5 DMPS	5/6	83

8	LEW + 75.0 BAL ^c	8/12	67
9	LEW + 37.5 BAL	3/6	50

^a In the tables of this paper, the data represent the combined results of a number of separate experiments. This was done to save space. The reason for the number of animals in some groups differing from the number in other groups of the same table is that very often the combined data are the result of from 2-3 separate experiments. Otherwise, the experiments were performed under identical conditions. The survival recorded in this table is that for 7 days after lewisite administration.

^b Lewisite (29.7 $\mu\text{mols/kg}$) was given sc at time zero.

^c All agents given sc except BAL, which was given im. Dimercapto compounds given at +1 min, +90 min, +180 min, +360 min after lewisite and at 8 a.m. and 4 p.m. on day 2 and 3. Administration of these amounts of dimercapto compound at the times cited above did not cause any fatalities in control animals that did not receive lewisite (data not shown).

^d Pair-wise comparisons: $p < 0.0001$ for 1 vs 2; $p = 0.0001$ for 1 vs 3 and 1 vs 4; $p < 0.001$ for 1 vs 6 and 1 vs 7; $p = 0.001$ for 1 vs 8 and 0.01 for 1 vs 9.

vented chemical exhaust hood. Safety glasses and thick neoprene gloves were worn.

The stability of DMPS, DMSA or BAL was determined using iodometric titration. To 2.50 ml of a 0.10 M dimercapto solution, 10 drops of starch indicator solution were added. The solution was titrated using 0.025 N iodine solution until the blue color appeared and persisted for at least 10 sec.

Results

Anti-Lewisite Activity

The data of Table 1 clearly show that both DMSA and DMPS have anti-lewisite activity when given subcutaneously. As little as 20 μ moles/DMSA/kg administered sc, according to the stated regimen, protects against the lethal actions of lewisite. Thus, DMSA and DMPS are analogous to BAL not only in chemical structure but also with respect to anti-lewisite activity. In addition, DMSA and DMPS have anti-lewisite activity when given orally (Table 2).

TABLE II

Meso-Dimercaptosuccinic Acid or 2,3-Dimercapto-1-Propanesulfonate is effective, when given by mouth, in protecting rabbits against the lethal effects of Lewisite

Group	μ moles/kg	survive/start	% survival
1	LEW ^a + -----	0/12	0
2	LEW + 400 DMSA ^b	5/6	83
3	LEW + 200 DMSA ^b	4/6	67
4	LEW + 400 DMPS ^b	6/6	100
5	LEW + 200 DMPS ^b	4/6	67

6	LEW + -----	1/6	17
7	LEW + DMSA ^c	4/6	67
8	LEW + DMPS ^c	1/6	17

^a Lewisite (29.7 μ moles/kg) was given sc at time zero.

^b Dimercapto compounds given po at -45, -2, +90 and +300 min. after lewisite and 8 a.m. and 4 p.m. on day 2 and 3. No fatalities occurred in control animals that received these amount of dimercapto compound, po, (but no lewisite) at the times cited above. Survival was followed and recorded for 7 days after lewisite administration.

^c Dimercapto compounds given po as follows: 400 μ moles of dimercapto compound /kg at 5 min before lewisite, and 200 μ moles/kg at each of the following times after lewisite: 1 hr., 2.5 hrs. and 5 hrs. on the first day plus 8 a.m. and 4 p.m. on day 2 and 3.

^d For pair-wise comparison: $p = 0.001$ for 1 vs 2; $p = 0.01$ for 1 vs 3; $p < 0.001$ for 1 vs 4 and $p = 0.01$ for 1 vs 5

Additional studies have demonstrated that a single po administration of DMSA (400 μ moles/kg) 15 min prior to lewisite was ineffective since only 1 of 6 animals survived for 7 days. In the experiments of Table 1 and 2, most of the rabbits that received lewisite and no dimercapto therapy died within 12 hrs. If animals died after receiving lewisite plus dimercapto therapy, they usually died between the first and fifth day of the experiment.

Stability Studies

The stabilities of DMSA, DMPS and BAL in 0.10M solutions at pH 5.0 and 7.0 were examined (Fig 1). The mercapto groups of these compounds, in aqueous solutions at pH 5.0, are stable (Fig 1). Even after 7 days at room temperature, from 78 to 87% of the mercapto groups remain titratable. At pH 7.0, however, the greater stability of DMSA is evident with 82% of the mercapto groups remaining after 7 days.

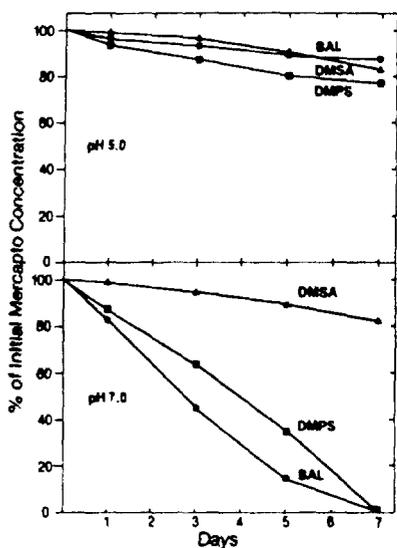


FIG. 1

Stability of DMSA, DMPS and BAL at pH 5.0 or 7.0. Aqueous solutions of each compound were prepared, adjusted to pH 5.0 or 7.0 and to a final concentration of 0.10mmol/ml. Solutions were prepared using double-distilled H₂O and maintained at 24°. Aliquots were removed at indicated times and the mercapto content determined. Each value shown is the average of two separate titrations.

By this time and under these conditions none of the mercapto groups of DMPS or BAL remained. Other studies (data not shown) indicated that DMSA, in a solution of 5% NaHCO₃, when either frozen for 4 days or frozen and thawed each day for 4 days retained 82% of its original mercapto groups. If similar solutions were held at 4° or 24° for 4 days, DMSA retained 76% and 69% of its mercapto groups, respectively. Although solutions of DMPS in 5% NaHCO₃ were stable (92-95% of original) when either frozen, or frozen and thawed each day for 7 days, after three days at room temperature no titratable mercapto groups were evident.

Discussion

Extensive clinical experience with DMSA and DMPS as antidotes and prophylactics for mercury, lead, arsenic and other heavy metals has been

reported in Soviet and mainland Chinese literature (10,11,12,13). In the Soviet Union, DMPS has been for many years an official drug called Unithiol. Recently, there has been a great deal of interest in both of these water soluble chemical analogs of dimercaprol in the United States and abroad (14,15,16,17,18). This has resulted in the confirmation and extension (19,20,21,22) of earlier reports dealing with both the basic and clinical investigations of DMSA and DMPS.

Although dimercaprol is a name relatively easily identified in the field of therapeutics, the compound is known most commonly in other areas as British Anti-Lewisite. It seemed reasonable to expect that a true analog agonist might also have Anti-Lewisite Activity.

The present experiments clearly show that either DMSA or DMPS will protect rabbits against the lethal systemic effects of subcutaneously administered lewisite (Table 1 and 2). Therefore, DMSA and DMPS can be considered to be not only analogous in chemical structure but also in anti-lewisite activity. In addition, DMSA and DMPS are effective when given by mouth; a route not recommended for BAL administration.

The dose schedule for administering DMSA and DMPS was based on a three day regimen recommended in the literature for the use of these metal binding agents. Subsequent studies (Aposhian, unpublished) have demonstrated that as little as one dose of 40 μ moles/kg of either drug given im one minute after lewisite will result in the survival of 4 out of 6 rabbits. In addition when DMSA therapy is delayed until 90 min after lewisite, 6 of 6 rabbits, survived. The purpose of these studies was to determine whether DMSA or DMPS have anti-lewisite activity. No attempt has been made to quantitate their relative efficacy against lewisite.

Not only are these analogs crystalline and readily water soluble, they are less toxic than BAL. The results of a number of different investigations in rodents have led to the conclusion that the acute toxicity of DMSA is less than that of DMPS which is much less than that of BAL (19,23,24,25).

The stability studies (Fig 1) were initiated for two reasons. Many investigators believe that DMSA and DMPS are unstable because of their dimercapto structure. Since solutions of these compounds were being used throughout the day, for example see Table 1 and 2, it has been considered necessary by a number of investigators (17,20) to prepare solutions immediately before use. The stability of solutions of these dimercapto compounds is somewhat surprising since mercapto compounds are usually thought to be readily oxidized.

In addition to many older reports in the Soviet and Chinese literature (10,12,26) dealing with DMPS and DMSA in human therapy, such use has been strengthened by recent papers containing data from clinical investigations. For example, DMSA has been used recently in the treatment of a 46 yr. old man who ingested 2000 mg of arsenic in a suicide attempt (27). Treatment with 300 mg of DMSA every 6 hrs po for 3 days caused an increase in the urinary excretion of arsenic and eventual recovery. DMSA increased the excretion of lead in the urine of smelter workers and was effective in treating the signs and symptoms of lead poisoning (28). The dimercapto compound was well tolerated and no signs of toxicity were evident. The usefulness of DMPS and other metal binding agents in the treatment of mercury intoxication resulting from the Iraqi mercury disaster has been documented recently (18). DMPS, as DIMAVAL, is now an approved drug in West Germany for the treatment of mercury poison. These two water soluble analogs of BAL, analogous in activity as well

as chemical structure, active when given by mouth and of low toxicity, warrant continued investigation as possible replacements for BAL.

Acknowledgements

The authors wish to express their sincere appreciation to Mrs. Linda Boxhorn for her excellent technical assistance; to Heyl and Co. for supplying the DMPS (DIMAVAL[®]); and to Johnson and Johnson for the gifts of DMSA. One of the authors (C.A.H.) was the recipient of a Heyl & Co. postdoctoral fellowship. The assays for lewisite purity were performed by Linda Szafraniec and Paul M. Davis. The authors are indebted to Dr. Thomas E. Moon of the University of Arizona Cancer Center Division for statistical analysis. This work was supported by contract DAMD17-8-C-0052 from the USAMRDC.

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BIOLOGICAL CHELATION: 2,3-
DIMERCAPTO-
PROPANESULFONIC ACID AND
MESO-DIMERCAPTOSUCCINIC
ACID

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INTRODUCTION

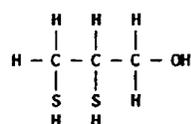
In 1946, summaries of the results of experiments dealing with a new metal binding agent appeared in the biomedical literature. The agent became known as British Anti-Lewisite or BAL. In the U.S. it was given the generic name of dimercaprol. Its importance initially was its effectiveness in treating exposure to the arsenic-containing chemical warfare agent, lewisite. Within a short time, BAL was shown to be useful in the treatment of intoxication by arsenic, lead, mercury and a number of other heavy metals. It was considered to be the long-sought universal antidote for poisoning by one or more of the heavy metals.

In subsequent years due to the increasing clinical experience and to the continuing search for better therapeutic agents, other chelating agents have been introduced (1). Some of these metal-binding agents have replaced one or more of the uses of BAL in clinical medicine. For example D-penicillamine is used to increase the excretion of copper in Wilson's disease (2) and N-acetyl-DL-penicillamine to treat mercury intoxication (3). The exception has been in the treatment of arsenic poisoning. Since the late 1940s, BAL has remained the drug of choice in the U.S. for treating arsenic poisoning (1). BAL, however, is far from the ideal drug. Some of its limitations are listed in Table I.

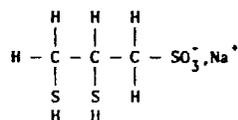
In the mid-1950s, the chelating properties of two new agents, the sodium salt of 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-dimercaptosuccinic acid (DMSA) were reported (4, 5). These compounds are water soluble analogs of BAL whose structures are shown in Figure 1. The synthesis and some of the metal binding properties of DMPS were reported in 1956 by Strunkin (4). DMPS is an official drug of the Soviet Union where it is known as Unithiol. The use of DMSA to increase the uptake of antimony during schistosomiasis therapy was reported by Friedheim *et al.*, (5) in 1954. For the

TABLE I. SOME LIMITATIONS OF BRITISH ANTI-LEWISITE

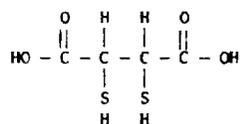
-
1. High toxicity
 2. Low therapeutic index
 3. Unpleasant side effects
 4. Limited water solubility
 5. Instability in aqueous solution
 6. Must be given by injection
-

WATER SOLUBLE AND ORALLY ACTIVEANALOGS OF BRITISH ANTI-LEWISITE

BAL
(BRITISH ANTI-LEWISITE)



DMPS
(2,3-DIMERCAPTO-1-PROPANE-
SULFONIC ACID, Na SALT)
UNITHIOL, DIMAVAL



DMSA
(MESO-DIMERCAPTO SUCCINIC ACID)
SUCCTMER

FIG. 1. Water soluble and orally active analogs of British Anti-Lewisite.

next 20 years, many reports about the usefulness of these two dimercapto compounds appeared in the biomedical literature of the Soviet Union and mainland China. A few examples of these are cited (6-11). During this time, studies of these compounds by western investigators appear to be virtually nonexistent. (For example, it was not until 1975 that Friedheim and Corvi (12) reported the effectiveness of DMSA in treating mercury poisoning and it was not until 1976 that Gabard (13) reported the use of DMPS in mercury chelation therapy). The reasons for the paucity of earlier studies in the West may be that the synthesis of DMPS is very difficult and its export from the

Soviet to the West was prohibited. In the case of DMSA, although its synthesis is not as difficult, the main reason for a lack of investigative studies in the West appears to be that interest in and funds for chelation research were very limited. DMSA is called Succimer in the Soviet literature.

In about 1978, Heyl & Co., Berlin, succeeded in synthesizing and producing DMPS. This recent availability has encouraged investigators in West Germany, Norway and the U.S. to "rediscover" and study the drug with renewed interest (13-19). DMPS is marketed by Heyl & Co., as Dimaval. It is an approved drug in West Germany for the treatment of mercury intoxication. With the increasing need for safe and convenient chelating agents in clinical medicine, Dimaval should become an important addition to the physician's armamentarium.

The present paper summarizes experiments in this laboratory dealing with the experimental use of DMPS and DMSA in the treatment of poisonings of the following kinds: sodium arsenite in mice, lewisite in rabbits and cadmium chloride in mice. In addition, a summary of some of the important properties of DMPS and DMSA that has been retrieved from the Soviet literature will be discussed.

MATERIALS AND METHODS

Animals. Male mice of the Swiss CDI strain (randombred Albino) were used in most of the experiments unless otherwise noted. At the time they were used in the experiments, they weighed approximately 25-30 g. Their source of purchase, their food and conditions for maintaining them have been described previously (16, 20).

Chemicals. DMPS in the form of its Na salt was a gift of Heyl & Co., Berlin. Since each molecule of NaDMPS has a molecule of H₂O associated with it, a molecular weight of 228.2 was used in mol calculations. DMSA used for the rabbit studies was pharmaceutical grade and a gift of Johnson and Johnson. The source of the other compounds have been described elsewhere (16, 20).

Biological studies. The assay of agents that bind and/or mobilize heavy metals can be based on a number of different measurable responses. The basis of one type of assay is the prevention or reversal of the lethal or toxic effects of the particular heavy metal. A second assay is based on the increased excretion of the metal by the putative metal binding agent. There is, however, increasing evidence that supports still another mechanism. Namely, a metal binding agent sometimes forms an insoluble metabolically-inert complex with the metal. The complex, because of its insolubility, is not excreted from the body. It remains in the cell, metabolically-inert and non-toxic. Therefore, it is possible that some metal binding agent might be life saving without increasing excretion of the metal. This mechanism has been proposed to explain the effectiveness of N-acetyl-DL-penicillamine (21). For these reasons we chose, as

the basis of our initial assays in the present work, the prevention of the lethal action of NaAsO_2 . Eventually a quantitative comparison will be made of these agents as to their influence on the excretion of ^{74}As .

The concentrations of the NaAsO_2 solutions were prepared so that a 25 g animal would receive 0.050 ml. To quantitate the relative effectiveness of a compound in protecting against the lethal effects of NaAsO_2 , the influence of the administration, i.p., of that compound on the LD_{50} of NaAsO_2 was determined by injecting, s.c., various amounts of NaAsO_2 dissolved in 0.9% saline. Solutions of the mercapto compounds were prepared immediately before use in 0.9% saline, adjusted to pH 5.5 using NaOH and the concentration adjusted so that a 25 g mouse would receive 0.10 ml. Injections were made using a 0.25 ml glass syringe with a No. 26 needle of 1/2 inch length. For oral administration, curved 18 gauge oral feeding needles, purchased from Popper & Sons, New Hyde Park, N.Y., were used. BAL was dissolved in peanut oil unless otherwise stated.

Statistical analysis. When appropriate, experimental results were analyzed using quantal response methodology. A logistic regression model was used to fit the experimental data and parameters were estimated using the BMDP program package (22) on a CDC Cyber 175 digital computer. Median effective dose and corresponding 95% confidence intervals were estimated following Finney (23).

RESULTS AND DISCUSSION

DMPS or DMSA Protects Mice Against the Lethal Effects of Sodium Arsenite

Mice injected with 0.14 mmols NaAsO_2/kg (an approximate LD_{100} dose) and saline, in lieu of mercapto compounds, did not survive (Table 2). The deaths occurred within 48 hr after arsenic administration. DMPS and DMSA are potent antidotes (Table 2) when either agent is given intraperitoneally immediately after NaAsO_2 . However, two other well-known and clinically useful chelating agents, D-penicillamine and N-acetyl-DL-penicillamine, do not protect (Table 2) under these conditions. The results with these two sulfhydryl compounds are unexpected since there have been two reports of the usefulness of penicillamine in the therapy of arsenic poisoning of humans (24-26).

Neither DMPS nor DMSA need be given immediately after NaAsO_2 . The administration of either one of the compounds can be delayed at least 2 hr and still be effective (Table 3).

Of greater importance for any therapeutic or prophylactic potential is that DMPS or DMSA is effective even when given orally 15 min prior to the administration of the arsenic compound (Table 4). Under the present experimental conditions, they are effective as oral prophylactics against arsenic intoxication.

TABLE 2. PROTECTION BY DMPS OR DMSA AGAINST THE LETHAL EFFECTS OF SODIUM ARSENITE (16)

Chelating agent* (mmoles/kg) i.p.	Cumulative 21-day survival No. surviving/No. started	%
(Saline)*	0/48	0
0.80 DMPS	32/32	100
0.40 DMPS	12/12	100
0.25 DMPS	24/24	100
0.14 DMPS	21/24	87.5
0.07 DMPS	19/24	79
0.25 BAL	22/24	92
0.14 BAL	2/24	8
0.25 DMSA	24/24	100
0.14 DMSA	20/24	83
0.07 DMSA	16/24	67
0.80 D-Pen	0/12	0
0.25 D-Pen	0/12	0
0.80 N-Ac-DL-Pen	0/12	0
0.25 N-Ac-DL-Pen	0/12	0

*The NaAsO₂ (0.14 mmoles/kg) was injected s.c. in the right rear leg.

†The chelating agents were administered i.p. immediately after NaAsO₂.

In this and subsequent Tables, the data represent the combined results of a number of separate experiments. The data were combined to take advantage of the resulting larger number of animals for the calculation of median doses, the statistical evaluation of data and the more economical use of publication space. Thus, the reason for the number of animals in some groups differing from the number in other groups of the same Table is that very often the combined data are the result of from 2 to 4 separate experiments in which different numbers of animals were used in each experiment. Otherwise, the experiments were performed under identical conditions. None of the mercapto compounds listed in Table 2 are toxic at the doses used and under the conditions of the present experiments.

TABLE 3. EXPERIMENTAL THERAPY WITH DMPS OR DMSA CAN BE DELAYED AFTER ARSENIC POISONING (16)

Dithiol and time after NaAsO ₂ * was given	Cumulative 21-day survival No. surviving/No. started	%
(Saline)	0/20	0
0.25 DMPS		
at 60 min	16/19	84
at 90 min	18/19	95
at 120 min	17/20	85
0.25 DMSA		
at 60 min	15/19	79
at 90 min	19/20	95
at 120 min	11/20	55

*All animals received NaAsO₂ (0.14 mmoles/kg) s.c. in the right rear leg. DMPS and DMSA were given i.p. At the start of the experiment, when NaAsO₂ was given, there were 10 animals in each group. However, in 3 of the experimental groups, one animal died before DMPS or DMSA was administered. Therefore, those groups are listed with 19 instead of the 20 started.

TABLE 4. PROPHYLACTIC AND ORAL ACTIVITY OF DMPS OR DMSA (16)

Thiol compound (mmoles, kg) oral	Cumulative 21-day survival		%
	No. surviving	No. started	
Saline	0	28	0
1.0 DMPS*	16	18	89
0.75 DMPS	8	10	80
0.50 DMPS	16	20	80
0.25 DMPS	17	20	85
0.12 DMPS	0	10	0
1.0 DMSA	8	8	100
0.50 DMSA	10	10	100
0.25 DMSA	8	10	80
0.12 DMSA	4	10	40

The NaAsO_2 (0.14 mmoles/kg) was administered s.c. in the right rear leg. DMPS or DMSA was given orally 15 min prior to the NaAsO_2 .

*The survival of control animals receiving 1.0 mmoles of DMPS per kg and saline, instead of NaAsO_2 , was 100%.

The experiments summarized in Tables 2 to 4 demonstrate the effectiveness of DMPS and DMSA in protecting mice against the lethal action of arsenic. There does not appear to be a great difference between the effectiveness of these two agents under the present conditions. However, it is clear that D-penicillamine and N-acetyl-DL-penicillamine are without beneficial properties against the lethal effects of arsenic under the conditions used in these experiments. Although to our knowledge, arsenic chelate stability constants have not been determined for DMPS or DMSA, such constants, as well as the influence of DMPS in stimulating arsenic excretion, would be valuable in designing and determining the most effective chelating agent for therapy of arsenic poisoning.

Meanwhile, the relative effectiveness of a number of metal binding agents, with particular emphasis on DMPS and DMSA, has been evaluated quantitatively by determining their activity in changing the LD_{50} of NaAsO_2 in mice. In addition, the therapeutic index of DMPS and DMSA has been determined.

DMPS or DMSA increases the LD_{50} of NaAsO_2

The LD_{50} of subcutaneously administered NaAsO_2 was found to be 0.132 and 0.127 mmol/kg in 2 separate experiments. When the data of the 2 experiments were combined and used to determine the LD_{50} , it was found to be 0.129 mmol/kg (Table 5). The curve is remarkably steep, having a slope of 40.76, if the proportion survival vs dose model is used. The animals that did not survive usually died within 3 days after injection.

TABLE 5. LD₅₀ OF SODIUM ARSENITE IN THE MOUSE (20)

NaAsO ₂ (mmol/kg, s.c.)	Exp. 1 Dead Started	Exp. 2 Dead Started	Summation Dead Started
0.08	0/8	—	0/8
0.09	0/8	—	0/8
0.10	0/8	0/12	0/20
0.11	0/8	—	0/8
0.12	1/8	2/12	3/20
0.13	3/8	7/12	10/20
0.14	7/8	12/12	19/10
0.16	—	12/12	12/12
LD ₅₀ (mmol/kg) 95% Confidence interval	0.1315 (0.122, 0.260)	0.1274 (0.080, 0.131)	0.1290 (0.125, 0.139)

One way of quantitating the activity of a drug in overcoming the toxicity of a toxic agent is to determine how much the LD₅₀ of the toxic agent is increased by giving more of the potential therapeutic drug. That is, the toxicity of the toxic agent should decrease by giving the therapeutic agent. When 2 i.p. injections of DMPS (0.80 mmols DMPS/kg/injection) are given, one immediately following and the other 90 min after the NaAsO₂, the LD₅₀ of NaAsO₂ is increased approximately 4.2-fold to 0.538 mmol/kg (Table 6). Under the same conditions, but using DMSA instead of DMPS, the LD₅₀ of NaAsO₂ is increased about 4.4-fold to 0.573 mmol/kg (Table 6). The increase with DMSA is only about 5% more than when DMPS is given. Since the LD₅₀ of NaAsO₂ plus DMPS falls within the confidence interval of the LD₅₀ of NaAsO₂ plus DMSA, it appears that the effect of DMPS and DMSA on the LD₅₀ of NaAsO₂ is essentially the same under these experimental conditions.

Determination of Therapeutic Index

It was also of interest to determine and compare the therapeutic index of DMPS and DMSA as a measure of their relative potency. The therapeutic index under these conditions was determined by dividing the LD₅₀ of the dimercapto compound by its ED₅₀. The latter value is defined as the amount of dimercapto compound (mmol/kg) protecting 50% of the animals against the lethal effects of 0.15 mmol NaAsO₂/kg. The latter dose kills 100% of the animals in this laboratory.

The LD₅₀ of DMPS, when given i.p., was found to be 5.22 mmols/kg (Table 7). This value is comparable to the value of 5.57 mmols/kg obtained by Kostygov (9) and 5.02 mmols/kg, i.p., in rats, as reported recently by Planas-hne *et al.* (27). For DMSA, the LD₅₀ is 13.58 mmols/kg (Table 8). It compares favorably with 12.1 mmols/kg, i.p., found in mice by Shih-Chun *et al.* (11) in Shanghai and Peking and 14.0 mmols/kg determined by Matsuda

TABLE 6. DIMERCAPTO-1-PROPANE SULFONATE OR MESO-DIMERCAPTOSUCCINIC ACID INCREASES THE LD₅₀ OF SODIUM ARSENITE* (20)

NaAsO ₂ (mmol/kg, s.c.)	DMPS	DMSA
	No. Dead No. Started	No. Dead No. Started
0.35	0/12	2/24
0.40	5/24	8/24
0.45	0/12	8/36
0.46	2/12	—
0.50	8/24	5/24
0.55	13/24	11/36
0.60	18/24	15/36
0.65	—	10/12
0.70	23/24	33/36
0.75	—	12/12
LD ₅₀ (mmol/kg)	0.538	0.573
95% Confidence interval	(0.492, 0.590)	(0.443, 0.708)

*DMPS or DMSA, 0.80 mmol/kg, was given, i.p. immediately after and 90 min after NaAsO₂.

TABLE 7. LD₅₀ OF DIMERCAPTOPROPANESULFONATE IN MICE (20)

DMPS (mmols/kg, i.p.)	Dead Started
3.3	0/8
4.0	0/8
5.0	7/16
5.5	5/8
6.0	7/8
6.6	15/16
7.0	8/8
9.9	8/8
LD ₅₀ (mmols/kg)	5.22
95% Confidence interval	(4.35, 5.51)

(10) in Japan. An LD₅₀ in excess of 16.5 mmols/kg has been reported by Friedheim and Corvi (12). It is not clear whether this latter higher value is due to a difference in the mouse strains used or is due to a higher purity of DMSA. When mice were given NaAsO₂ (0.15 mmol/kg) s.c. and 10 min later were treated, i.p., with different amounts of DMPS, the ED₅₀ was found to be 0.066 mmol/kg (Table 9). The ED₅₀ under these conditions for DMSA was 0.065 mmol/kg. The therapeutic index for DMPS or DMSA under these conditions

TABLE 8. LD₅₀ OF MESO-DIMERCAPTOSUCCINIC ACID IN MICE (20)

DMSA (mmols, kg, i.p.)	Dead Started
6.0	0/32
12.0	8/32
13.0	6/12
14.0	9/12
16.0	19/24
18.0	17/20
24.0	32/32
LD ₅₀ (mmols/kg)	13.58
95% Confidence interval	(11.36, 15.22)

TABLE 9. DETERMINATION OF THE ED₅₀ AND THERAPEUTIC INDEX OF 2,3-DIMERCAPTO-I-PROPANE SULFONIC ACID, NaSALT, AND MESO-DIMERCAPTOSUCCINIC ACID WHEN GIVEN 10 OR 35 MIN AFTER 0.15 mmols NaAsO₂/kg (20)

Dimercapto agent (mmol/kg, i.p.)	DMPS + 10 min	DMSA + 10 min	DMPS + 35 min	DMSA + 35 min
	number surviving/number started			
0.010	—	0/24	—	0/12
0.015	0/36	—	3/36	—
0.030	1/36	5/24	7/36	1/30
0.040	—	6/24	—	—
0.045	6/24	—	8/24	—
0.050	—	10/24	—	—
0.060	6/24	13/24	18/24	5/38
0.0675	15/24	—	—	—
0.070	—	9/12	—	—
0.075	21/24	—	—	—
0.080	—	18/24	—	5/12
0.090	20/24	—	15/24	3/10
0.100	—	—	—	16/28
0.105	31/36	—	30/36	—
0.120	35/36	—	34/36	8/12
0.125	—	21/24	—	13/17
0.150	—	—	—	21/30
0.160	—	—	—	6/8
0.200	—	—	—	37/46
0.300	—	—	—	35/38
ED ₅₀ (mmol/kg)	0.066	0.065	0.061	0.119
Confidence interval	(0.059-0.072)	(0.040-0.086)	(0.048-0.072)	(0.071-0.164)
Therapeutic index	79	209	86	115

was 79 and 209, respectively. When the DMPS and DMSA was given 35 min after the NaAsO_2 , the therapeutic index was found to be 86 and 115, respectively. As can be seen under these conditions, DMSA can be considered to be a more effective agent than DMPS in protecting mice against the lethal effects of NaAsO_2 under these conditions.

Other metal binding agents were also tested for their activity in protecting against the lethal effects of NaAsO_2 . Neither D-pen nor N-Ac-DL-Pen changes the LD_{50} of NaAsO_2 significantly at the 95% level of significance (Table 10). Other agents (data not shown) that were also found to be ineffective in this respect are the sodium salt of diethyldithiocarbamate, α -mercaptopropionylglycine, DL-N-acetylhomocysteinethiolactone, and monomercaptosuccinic acid.

TABLE 10. NEITHER D-PENICILLAMINE NOR N-ACETYL-DL-PENICILLAMINE INCREASED THE LD_{50} OF SODIUM ARSENITE (20)

	none	D-Pen*	N-Ac-DL-Pen*
NaAsO_2 (mmols/kg. s.c.)	<u>Dead</u> <u>Started</u>	<u>Dead</u> <u>Started</u>	<u>Dead</u> <u>Started</u>
0.10	0/12	0/8	0/8
0.12	2/12	5/8	1/8
0.13	7/12	7/8	5/8
0.14	12/12	8/8	4/8
0.16	12/12	8/8	8/8
0.20	—	8/8	8/8
LD_{50} (mmol/kg)	0.127	0.119	0.133
95% Confidence interval	(0.080-0.131)	(0.078-0.191)	(0.054-0.142)

*D-pen or N-Ac-DL-pen (0.80 mmols/kg) was given, i.p., immediately following and at 90 min after the metal binding agent.

DMPS and DMSA Have Anti-Lewisite Activity

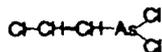
The name British Anti-Lewisite is ingrained very firmly in the mind of most biomedical investigators and physicians. One of the reasons for this is that most medical students and biomedical graduate students are told, in class, at one time or another, of the rational discovery and development of this metal chelating agent as an antidote for lewisite. This almost necessitates that any compound proposed as a replacement of BAL be shown to have anti-lewisite activity. Thus, we have tested DMPS and DMSA for their activity in protecting against the lethal effects of lewisite. The experiments were begun last March in collaboration with Drs. Brennie Hackley, Millard Mershon and Mr. Floyd Brinkley at the BioMed Laboratory at Aberdeen.

Lewisite is an arsenic containing CW agents. It is an oily liquid at 20°. It causes blisters, tissue destruction and blood vessel injury. Systemic poisoning

leading to death is possible. As a CW agent, it is considered to be a moderately delayed casualty agent. Its chemical formula is shown in Figure 2.

Since the introduction of British Anti-Lewisite at the beginning of World War II, all of the therapy of prophylaxis of lewisite has been aimed at chelating the arsenic in the molecule and making it biologically unavailable. This was the basis of Sir Rudolph Peters' search for British Anti-Lewisite.

In the present experiments, the rabbit is anesthetized and then shaved. Using a microliter syringe, lewisite ($29.7 \mu\text{mols/kg}$) is injected s.c. The volume of lewisite injected usually amounted to between 7 and 11 μl , depending on the weight of the animal. Table II shows that either DMSA or DMPS will protect rabbits against the lethal effects of lewisite. Using lewisite alone, none of the 6 animals survived. If the animals received 75 $\mu\text{mols DMSA/kg}$ at the times indicated, all of the animals survived. DMSA protects against the lethal systemic effects of lewisite. In the second experiment, only 1 of 6 animals receiving lewisite survived; 66% survived when receiving the 75 $\mu\text{mols DMPS/kg}$ regimen; and 50% of those receiving BAL survived. We do not wish to imply that the effectiveness of these agents against lewisite is in the order of $\text{DMSA} > \text{DMPS} > \text{BAL}$. More data are needed before relative effectiveness can be stated.



LEWISITE

(2-CHLOROETHENYL)- ARSONOUS DICHLORIDE

FIG. 2. Chemical formula for lewisite.

TABLE II. DMSA OR DMPS WILL PROTECT RABBITS AGAINST LETHAL EFFECTS OF LEWISITE

Expt.	$\mu\text{mols/kg}^*$	7-day survival survival: start	%
I	LEW + —	0/6	0
	LEW + 75 DMSA	6/6	100
II	LEW + —	1/6	17
	LEW + 75 DMPS	4/6	66
	LEW + 75 BAL	3/6	50

*All agents were given s.c. except BAL, which was given i.m. The stated amount of dimercapto compounds were given at +1', +90', +180', +360' after lewisite and a.m. and p.m. on day 2 and 3. †29.7 $\mu\text{mols lewisite/kg}$. These experiments were performed in collaboration with Drs. B. Hackley, M. Mershon and Mr. F. Brinkley.

The data, however, clearly show that DMSA or DMPS will protect rabbits against the lethal effects of lewisite. In this respect the compounds can be said to have Anti-Lewisite activity.

Treatment of Cadmium Toxicity

Cadmium is virtually ubiquitous. It is deposited and accumulates in most body tissues. It is found in all environmental compartments (air, soil, food and water). The study of cadmium biology has been stimulated by the debilitating osteoporosis of Itai-Itai disease in Japanese adults and the awareness that the increased use of cadmium in industrial and agricultural processes has greatly increased the prevalence of cadmium in the environment (28-30). Along with this, there has been an increased incidence of both acute and chronic cases of clinically identifiable cadmiosis (31). In the U.S., although the cadmium content of the human fetus is about 1 μ g, the body burden increases approximately 30,000-fold (to about 30 mg) by age 50 years (32).

In experimental acute cadmium poisoning, DTPA or EDTA are marginally effective (30, 33-37) and dimercaptopropanol is contraindicated (37-39). It is astonishing that no accepted dependable effective drugs have become available for treatment of cadmium intoxication, especially since the biological effects of cadmium have been studied intensively during the last 20 years. Thus a number of research groups have been involved recently in a search for an agent to treat cadmium intoxication (18, 30, 41).

I would like to present in a very brief manner some of the unpublished results of my laboratory group as to attempts to find a therapeutically useful cadmium binding agent. DMPS protects mice against the lethal action of cadmium chloride (Tables 12, 13 and 14). Multiple ligand therapy, however, involving CdCl_2 , DMPS and EDTA is ineffective. These observations (Tables 13 and 14) confirm those of Planas-Bohne (41) and to some extent those of Jones *et al.* (18).

In Table 14 are summarized the results with penicillamine and its analogs. Under the conditions of these experiments neither penicillamine nor any of its analogs so tested were active in protecting against cadmium lethality. Recent work by Yoshida *et al.* (40) with peptide fragments of mouse metallothionein is encouraging and should be extended to test peptide analogs of metallothionein fragments. Our own results are only a beginning and all studies with cadmium lethality and its therapy should be followed by kidney function tests.

Clinical Effectiveness in Man

Obviously the results of experiments summarized here and elsewhere warrant the continued investigation of these metal binding agents and their

TABLE 12. DMPS PROTECTS MICE AGAINST LETHAL ACTION OF CADMIUM CHLORIDE BUT MULTIPLE LIGAND THERAPY IS INEFFECTIVE

Group	CdCl ₂ (mmol/kg) (i.p.)		Chelator(s) (mmol/kg) (i.m.)	Cumulative 28-day survival No. surviving, No. started	%
I	0.06	+	(saline)	13/56	23
II	0.06	+	1.0 DMPS	19/20	95
III	0.06	+	0.4 DMPS	12/20	60
IV	0.06	+	0.2 DMPS	6/30	20
V	0.06	+	0.50 CaNa ₂ EDTA	12/18	67
VI	0.06	+	0.10 CaNa ₂ EDTA	8/20	40
VII	0.06	+	0.05 CaNa ₂ EDTA	4/18	22
VIII	0.06	+	1.0 DMPS & 0.50 CaNa ₂ EDTA	10/10	100
IX	0.06	+	0.40 DMPS & 0.10 CaNa ₂ EDTA	2/12	17
X	0.06	+	0.20 DMPS & 0.10 CaNa ₂ EDTA	3/12	25
XI	0.06	+	0.20 DMPS & 0.05 CaNa ₂ EDTA	3/10	30
XII	(saline)	+	1.00 DMPS	9/10	90

*The i.m. injections were given 60 min after the i.p. injection of Cd.

†The one animal that did not survive in this group died on Day 21. Death appeared to be the result of fighting.

‡When saline was given i.p. instead of CdCl₂ and any of the following were given i.m. (mmol/kg) the survival was 100%: DMPS (0.80) or (0.20); CaNa₂EDTA (0.50) or (0.05); DMPS (1.0) & CaNa₂EDTA (0.5); DMPS (0.20) & CaNa₂EDTA (0.05).

TABLE 13. DMPS GIVEN ORALLY INCREASES THE SURVIVAL OF MICE RECEIVING CADMIUM CHLORIDE (0.06 mmol/kg) I.P.

Group	Time after CdCl ₂ that DMPS (1.0 mmol/kg)* was given orally (min)	Cumulative 28-day survival No. surviving, No. started	%
I	-†, -	1/16	6
II	+10, +90,	10/16	62
III	+10, +90,	13/15	87
IV	- , +90,	10/16	62
The following groups are controls and received saline in place of CdCl ₂			
V	+10, -	14/16	88
VI	+10, +90,	16/16	100
VII	- , +90,	16/16	100

*The amount of DMPS given at each time.

†If DMPS was not administered, saline was given in its place.

TABLE 14. NEITHER PENICILLAMINE NOR ITS ANALOGS PROTECT MICE FROM THE LETHAL EFFECTS OF CADMIUM

Group	CdCl ₂ (i.p.) (mmol/kg)	Thiol compound (oral) (mmol/kg)*	Min after CdCl ₂ that thiol compd.	Cumulative 28-day survival %
I	0.06	+ (saline)	—, —, —	2/32 6
II	0.06	+ 1.0 N-Ac-Pen	+10, +90, +180	1/8 13
III	0.06	+ 1.0 N-Ac-Pen	+10, +—, +—	0/8 0
IV	(saline)	+ 1.0 N-Ac-Pen	+10, +90, +180	8/8 100
V	0.06	+ 1.0 D-Pen	+10, +90, +180	15/16 94
VI	0.06	+ 1.0 D-Pen	+10, +—, +—	0/8 0
VII	0.06	+ 1.0 D-Pen	+10, +90, +—	1/8 12
VIII	(saline)	+ 1.0 D-Pen	+10, +—, +—	8/8 100
IX	(saline)	+ 1.0 D-Pen	+10, +90, +—	7/8 88
X	(saline)	+ 1.0 D-Pen	+10, +90, +180	7/8 88
XI	0.06	+ 1.5 N-Ac-thiolisoleuc	+10, +90, +180	0/8 0
XII	0.06	+ 1.0 N-Ac-thiolisoleuc	+10, +90, +180	3/16 19
XIII	(saline)	+ 1.5 N-Ac-thiolisoleuc	+10, +90, +180	6/8 75
XIV	0.06	+ 1.0 N-Ac-thiolisoleuc	+10, +—, +—	6/8 75
XV	(saline)	+ 1.0 B-thiolisoleuc	+10, +—, +—	3/8 38
XVI	(saline)	+ 1.0 B-thiolisoleuc	+10, +—, +—	9/9 100

*Amount given at each stipulated time.

†These results are the sum of 4 separate experiments.

clinical use in the treatment of heavy metal poisoning. There have been recent reports that confirm their effectiveness in human therapy. DMSA was found to be useful in the treatment of a 46 year-old man who ingested 2000 mg of arsenic in a suicide attempt (42). Treatment with 300 mg DMSA every 6 hr p.o. for 3 days caused an increase in the urinary excretion of arsenic with eventual recovery. DMPS has also been effective in human arsenic poisoning (Wager, personal communication). Friedheim *et al*, (43) in an extension of experiments with experimental animals have reported the effectiveness of DMSA in treating lead poisoning and that it increases the urinary excretion of lead in smelter workers. DMSA was well tolerated and no signs of toxicity were evident. The usefulness of DMPS in the Iraqi mercury disaster has been

TABLE 15. COMPARISON AND SUMMARY OF SOME OF THE INFORMATION ABOUT AND PHARMACOLOGICAL PROPERTIES OF DMPS AND DMSA

2,3-Dimercaptopropane-1-sulfonate, Na salt (DMPS, unithiol, dimaval)	Meso-2,3-dimercaptosuccinic acid (DMSA, Succimer)
1. Synthesized in 1950-51 at the Ukrainian Res. Inst. for Health-Chemistry by Petrunkin. Published in 1956 (4).	1. Friedheim, 1954, used Sb-DMSA to increase Sb uptake in schistosomiasis therapy (5). (Intensively studied by mainland Chinese, 1959, for therapy of occupational metal poisoning (11). Primary Soviet investigator since 1965 has been Okonishnikova (50).
2. Crystalline powder, readily soluble in water. Very stable during sterilization and long-term storage.	2. Crystalline powder. Must be brought to pH 5-5.5 before completely soluble in water. Stability during sterilization and long term storage unknown.
3. Low toxicity, well tolerated even for chronic use, but DMSA is less toxic (20).	3. Toxicity is about 2.5 times less than DMPS (20).
4. Major toxic effect of high dose is hypotension (6, 8).	4. Major toxic effect of high dose unknown at present.
5. Distributed in extracellular space, exclusively (14). Excretion is urinary and rapid (14). Metabolic involvement supposedly none.	5. Distribution in body compartments unknown at present.
6. Effective antidote for As, Hg, Sb, Ag, Au, Cu, Cr, Pb, Po, Co, (6, 7, 16, 20, 45-49)	6. Effective antidote for As, Pb, Hg, Zn (16, 20, 50-54)
7. Urinary excretion of Cu and Zn. Increase Fe, Co, Mn or Ni excretion, none or minimal (55).	7. Urinary excretion of Co, Fe, Mn, Cu, or Zn. none or minimal (43).
8. Increase bile flow.	8. Effect on bile flow unknown.
9. Therapeutic dose about 250 mg for 70 kg man.	9. Therapeutic dose from 0.5 to 2 g for 70 kg man.
10. Can be given by mouth, s.c., i.p., i.m., i.v. Only 30-40% of oral dose absorbed from g.i. tract.	10. Can be given by mouth, s.c., i.p., i.m., i.v. Indications of oral dose being completely absorbed from g.i. tract.

documented recently (44). In fact DMPS, as DIMAVAL, is an approved drug in West Germany for the treatment of mercury poisoning.

There are many reports in the Soviet literature dealing with DMPS and DMSA both in experimental conditions or for human therapy. Some of them are cited in the summary of the properties of these two very important metal binding agents listed in Table 15. Obviously, these two water soluble analogs of BAL that are advantageous as to overall effectiveness and low toxicity can be expected to replace virtually all the therapeutic uses of British Anti-Lewisite.

SUMMARY

Water soluble analogs of British Anti-Lewisite that are active orally and less toxic than BAL are now available. These agents are 2,3-dimercapto-1-propanesulfonic acid and meso-dimercaptosuccinic acid. Evidence for their effectiveness in preventing the lethal effects of sodium arsenite in mice and lewisite in rabbits is presented. These analogs can be expected to replace BAL in the treatment of heavy metal poisoning.

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Mrs. Linda Boxhorn for her responsible and thoughtful technical assistance and to Heyl and Co. for supplying the DMPS (DIMAVAL). This work was supported by contract DAMD17-80-C-0052 from the USAMRDC. Much of the work reported from the author's laboratory has been published (16, 20).

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A. INGREDIENT NAME:

FERRIC SUBSULFATE PURIFIED POWDER

B. Chemical Name:

Approximately $\text{Fe}_2(\text{SO}_4)_3(\text{OH})_2$

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Feric Subsulphate (variable)

E. Information about how the ingredient is supplied:

Off white to pale yellow to brown fine powder, is odorless.

F. Information about recognition of the substance in foreign pharmacopeias:

The Pharmacopeia of the U.S.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

Topically

I. Information about strength:

J. Information about route of administration:

Topically

K. Stability data:

Decomposition: 520°C

L. Formulations:

M. Miscellaneous Information:

Please Refer to your P.O.# 54786 for the product listed below.

30-1328
54813

CHEMICAL NAME: FERRIC SUBSULFATE PURIFIED

CATALOG NUMBER: F1042

LOT NUMBER: LF0302

Seller certifies that the processes used in the manufacturing of the above items were in compliance with the applicable specifications as referred in or furnished with this purchase order.



Sincerely,

Lilian D. Casabar

12/97

LILIAN D. CASABAR
CofA COORDINATOR

enc /

QUALITY CONTROL REPORT

CHEMICAL NAME.: FERRIC SUBSULFATE POWDER A

MANUFACTURE LOT NO.: LF0302

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

E 1) DESCRIPTION.:

OFF WHITE TO PALE YELLOW TO BROWN FINE POWDER. IS ODORLESS.

2) SOLUBILITY.:

SLIGHTLY SOLUBLE IN WATER AND IN ALCOHOL.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) A SOLUTION RESPONDS TO THE TESTS FOR FERRIC.

PASSES.: _____

FAILS.: _____

COMMENTS.: PRODUCT GETS AFFECTED BY LIGHT AND AIR.

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

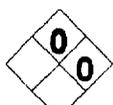
INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

Material Safety Data Sheet

NFWA	HMIS	Personal Protective Equipment
		
See Section 15.		

Section 1. Chemical Product and Company Identification		Page Number: 1
Common Name/ Trade Name	Ferric subsulfate	Code F3150
Manufacturer	SPECTRUM CHEMICAL MFG. CORP. 14422 SOUTH SAN PEDRO STREET GARDENA, CALIFORNIA 90248	CAS# 1310-45-8
Commercial Name(s)	Monse's Salt	RTECS Not available.
Synonym	Basic ferric sulfate	TSCA On the TSCA list.
Chemical Name	Not available.	CI# Not applicable.
Chemical Family	Salt.	IN CASE OF EMERGENCY CHEMTREC (24hr) 800-424-9300 Emergency phone: (310)516-8000
Chemical Formula	Fe ₄ (OH) ₂ (SO ₄) ₅	
Supplier	SPECTRUM QUALITY PRODUCTS, INC. 14422 SOUTH SAN PEDRO STREET GARDENA, CA 90248	

Section 2. Composition and Information on Ingredients					
Name	CAS #	Exposure Limits			% by Weight
		TWA (mg/m ³)	STEL (mg/m ³)	CEIL (mg/m ³)	
Ferric subsulfate	1310-45-8	1			100
Toxicological Data on Ingredients Ferric subsulfate LD50: Not available. LC50: Not available.					

Section 3. Hazards Identification	
Potential Acute Health Effects	Slightly dangerous to dangerous in case of ingestion. Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation.
Potential Chronic Health Effects	Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation. CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. The substance is toxic to blood, kidneys, liver. Toxicity of the product to the reproductive system: Not available. Repeated or prolonged exposure to the substance can produce target organs damage. WARNING: This product contains a chemical known to the State of California to cause cancer. Chemical ingredient(s) requiring this warning: NONE WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm. Chemical ingredient(s) requiring this warning: NONE

Section 4. First Aid Measures

Eye Contact	IMMEDIATELY flush eyes with running water for at least 15 minutes, keeping eyelids open. COLD water may be used
Skin Contact	NO known EFFECT according to our database.
Serious Skin Contact	No additional information.
Inhalation	Allow the victim to rest in a well ventilated area. Seek immediate medical attention.
Serious Inhalation	No additional information.
Ingestion	Remove dentures if any. Have conscious person drink several glasses of water or milk. INDUCE VOMITING by sticking finger in throat. Lower the head so that the vomit will not reenter the mouth and throat. NEVER give an unconscious person anything to ingest. Seek medical attention.
Serious Ingestion	No additional information.

Section 5. Fire and Explosion Data

Flammability of the Product	Non-flammable.
Auto-Ignition Temperature	Not applicable.
Flash Points	Not applicable.
Flammable Limits	Not applicable.
Products of Combustion	Not applicable.
Fire Hazards in Presence of Various Substances	Not applicable.
Explosion Hazards in Presence of Various Substances	Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available. No specific information is available in our database regarding the product's risks of explosion in the presence of various materials
Fire Fighting Media and Instructions	Non-flammable.
Special Remarks on Fire Hazards	No additional remark.
Special Remarks on Explosion Hazards	No additional remark.

Section 6. Accidental Release Measures

Small Spill	Use appropriate tools to put the spilled solid in a convenient waste disposal container. If necessary: Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements
Large Spill	Our database contains no additional information in case of a spill and/or a leak of the product. Use a shovel to put the material into a convenient waste disposal container. Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Section 7. Handling and Storage

Precautions	No specific safety phrase has been found applicable for this product.
Storage	No specific storage is required. Use shelves or cabinets sturdy enough to bear the weight of the chemicals. Be sure that it is not necessary to strain to reach materials, and that shelves are not overloaded.

Continued on Next Page

Section 8. Exposure Controls/Personal Protection

Engineering Controls	Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.
Personal Protection	Safety glasses. Lab coat.
Personal Protection in Case of a Large Spill	Splash goggles. Full suit. Boots. Gloves. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.
Exposure Limits	TWA: 1 (mg/m ³) from OSHA/NIOSH [1993] TWA: 1 (mg/m ³) from ACGIH [1993] Consult local authorities for acceptable exposure limits.

Section 9. Physical and Chemical Properties

Physical state and appearance	Solid.	Odor	Not available.
Molecular Weight	Not available.	Taste	Strong.
pH (1% soln/water)	4	Color	Brown.
Boiling Point	Not available.		
Melting Point	Decomposes.		
Critical Temperature	Not available.		
Specific Gravity	Not available.		
Vapor Pressure	Not available.		
Vapor Density	Not available.		
Volatility	Not available.		
Odor Threshold	Not available.		
Water/Oil Dist. Coeff.	Not available.		
Ionicity (in Water)	Not available.		
Dispersion Properties	See solubility in water.		
Solubility	Easily soluble in cold water, hot water.		

Section 10. Stability and Reactivity Data

Stability	The product is stable.
Instability Temperature	Not available.
Conditions of Instability	No additional remark.
Incompatibility with various substances	No specific information is available in our database regarding the reactivity of this material in presence of various other materials.
Corrosivity	Non-corrosive in presence of glass.
Special Remarks on Reactivity	No additional remark.
Special Remarks on Corrosivity	No additional remark.
Polymerization	No.

Section 11. Toxicological Information

Routes of Entry	Ingestion.
Toxicity to Animals	LD50: Not available LC50: Not available
Chronic Effects on Humans	The substance is toxic to blood, kidneys, liver. Toxicity of the product to the reproductive system: Not available.
Other Toxic Effects on Humans	Slightly dangerous to dangerous in case of ingestion. Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation.
Special Remarks on Toxicity to Animals	No additional remark.
Special Remarks on Chronic Effects on Humans	No additional remark.
Special Remarks on other Toxic Effects on Humans	No additional remark.

Section 12. Ecological Information

Ecotoxicity	Not available.
BOD5 and COD	Not available.
Products of Biodegradation	Some metallic oxides.
Toxicity of the Products of Biodegradation	The products of degradation are as toxic as the original product.
Special Remarks on the Products of Biodegradation	No additional remark.

Section 13. Disposal Considerations

Waste Disposal	Recycle to process, if possible. Consult your local or regional authorities.
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Section 14. Transport Information

DOT Classification	Not a DOT controlled material (United States).
Identification	Not applicable (PIN and PG).
Special Provisions for Transport	Not applicable.
DOT (Pictograms)	

Section 15. Other Regulatory Information and Pictograms

Federal and State Regulations	The following product(s) is (are) listed on TSCA: Ferric subsulfate
California Proposition 65 Warnings	WARNING: This product contains a chemical known to the State of California to cause cancer. Chemical ingredient(s) requiring this warning: NONE WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm. Chemical ingredient(s) requiring this warning: NONE
Other Regulations	OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200)

Continued on Next Page

Other Classifications	WHMIS (Canada)	Not controlled under WHMIS (Canada).
	DSCL (EEC)	Not controlled under DSCL (Europe)

HMIS (U.S.A.)		National Fire Protection Association (U.S.A.)	
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WHMIS (Canada) (Pictograms)	
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DSCL (Europe) (Pictograms)	
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TDG (Canada) (Pictograms)	
------------------------------	--

ADR (Europe) (Pictograms)	
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Protective Equipment	Lab coat
	Safety glasses.

Section 16. Other Information

Catalog Number(s) F1042

References Not available.

Other Special Considerations No additional remark.

Validated by E. Brull on 9/26/97.	Verified by E. Brull. Printed 9/29/97.
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Emergency phone: (310)516-8000

Notice to Reader
All chemicals may pose unknown hazards and should be used with caution. This Material Safety Data Sheet (MSDS) applies only to the material as packaged. If this product is combined with other materials, deteriorates, or becomes contaminated, it may pose hazards not mentioned in this MSDS. It shall be the user's responsibility to develop proper methods of handling and personal protection based on the actual conditions of use. While this MSDS is based on technical data judged to be reliable, Spectrum Quality Products, Inc. assumes no responsibility for the completeness or accuracy of the information contained herein.



Material Safety Data Sheet

NFPA	HMIS	Personal Protective Equipment
See Section 15.		

Section 1. Chemical Product and Company Identification		Page Number: 1
Common Name/ Trade Name	Ferric Sub sulfate Solution	Code F3155
Manufacturer	SPECTRUM CHEMICAL MFG. CORP. 14422 SOUTH SAN PEDRO STREET GARDENA, CALIFORNIA 90248	CAS# Not applicable.
Commercial Name(s)	Monsel's Solution	RTECS Not applicable.
Synonym	Not available.	TSCA All the ingredients are on the TSCA list
Chemical Name	Not applicable.	CI# Not applicable.
Chemical Family	Salt.	IN CASE OF EMERGENCY CHEMTREC (24hr) 800-424-9300 Emergency phone: (310)516-8000
Chemical Formula	Not applicable.	
Supplier	SPECTRUM QUALITY PRODUCTS, INC. 14422 SOUTH SAN PEDRO STREET GARDENA, CA 90248	

Section 2. Composition and Information on Ingredients					
Name	CAS #	Exposure Limits			% by Weight
		TWA (mg/m ³)	STEL (mg/m ³)	CEIL (mg/m ³)	
Ferric subsulfate	1310-45-8	1			20-22
Water	7732-18-5				78-80
Toxicological Data on Ingredients	Ferric subsulfate LD50: Not available. LC50: Not available.				

Section 3. Hazards Identification	
Potential Acute Health Effects	Very slightly to slightly dangerous in case of eye contact (irritant), of ingestion, of inhalation. Not dangerous in case of skin contact (non-corrosive for skin, non-irritant for skin, non-sensitizer for skin, non-permeator by skin).
Potential Chronic Health Effects	Very slightly to slightly dangerous in case of eye contact (irritant), of inhalation Not dangerous in case of skin contact (non-corrosive for skin, non-irritant for skin, non-sensitizer for skin, non-permeator by skin), of ingestion. CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. The substance is toxic to blood, kidneys, liver. Toxicity of the product to the reproductive system: Not available. Repeated or prolonged exposure to the substance can produce target organs damage. WARNING: This product contains a chemical known to the State of California to cause cancer. Chemical ingredient(s) requiring this warning: NONE

Continued on Next Page

WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.

Chemical ingredient(s) requiring this warning:

NONE

Section 4. First Aid Measures

Eye Contact	IMMEDIATELY flush eyes with running water for at least 15 minutes, keeping eyelids open. COLD water may be used.
Skin Contact	NO known EFFECT according to our database.
Serious Skin Contact	No additional information.
Inhalation	Allow the victim to rest in a well ventilated area. Seek immediate medical attention.
Serious Inhalation	No additional information.
Ingestion	Remove dentures if any. Have conscious person drink several glasses of water or milk. INDUCE VOMITING by sticking finger in throat. Lower the head so that the vomit will not reenter the mouth and throat. NEVER give an unconscious person anything to ingest. Seek medical attention.
Serious Ingestion	No additional information.

Section 5. Fire and Explosion Data

Flammability of the Product	Non-flammable.
Auto-Ignition Temperature	Not applicable.
Flash Points	Not applicable.
Flammable Limits	Not applicable.
Products of Combustion	Not applicable.
Fire Hazards in Presence of Various Substances	Not applicable.
Explosion Hazards in Presence of Various Substances	Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available. No specific information is available in our database regarding the product's risks of explosion in the presence of various materials.
Fire Fighting Media and Instructions	Non-flammable.
Special Remarks on Fire Hazards	No additional remark.
Special Remarks on Explosion Hazards	No additional remark.

Section 6. Accidental Release Measures

Small Spill	Dilute with water and mop up, or absorb with an inert DRY material and place in an appropriate waste disposal container. If necessary: Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.
Large Spill	Our database contains no additional information in case of a spill and/or a leak of the product. Absorb with an inert material and put the spilled material in an appropriate waste disposal. Neutralize the residue with a dilute solution of sodium carbonate. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Continued on Next Page

Section 7. Handling and Storage

Precautions	No specific safety phrase has been found applicable for this product.
Storage	No specific storage is required. Use shelves or cabinets sturdy enough to bear the weight of the chemicals. Be sure that it is not necessary to strain to reach materials, and that shelves are not overloaded.

Section 8. Exposure Controls/Personal Protection

Engineering Controls	Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value.
Personal Protection	Safety glasses. Lab coat. Gloves.
Personal Protection in Case of a Large Spill	Splash goggles. Full suit. Boots. Gloves. Suggested protective clothing might not be sufficient, consult a specialist BEFORE handling this product.
Exposure Limits	<p>Ferric subsulfate TWA: 1 (mg/m³) from OSHA/NIOSH [1993] TWA: 1 (mg/m³) from ACGIH [1993]</p> <p>Consult local authorities for acceptable exposure limits.</p>

Section 9. Physical and Chemical Properties

Physical state and appearance	Liquid.	Odor	Slight.
Molecular Weight	Not applicable.	Taste	Strong.
pH (1% soln/water)	4	Color	Brownish-red.
Boiling Point	100°C (212°F)		
Melting Point	Not available.		
Critical Temperature	Not available.		
Specific Gravity	1.58 (Water = 1)		
Vapor Pressure	17.535 mm of Hg (@ 20°C) based on data for: Water		
Vapor Density	0.62 (Air = 1) based on data for: Water		
Volatility	Not available.		
Odor Threshold	Not available.		
Water/Oil Dist. Coeff.	Not available.		
Ionicity (in Water)	Not available.		
Dispersion Properties	See solubility in water.		
Solubility	Easily soluble in cold water, hot water.		

Section 10. Stability and Reactivity Data

Stability	The product is stable.
Instability Temperature	Not available.
Conditions of Instability	No additional remark.
Incompatibility with various substances	No specific information is available in our database regarding the reactivity of this material in presence of various other materials.
Corrosivity	Non-corrosive in presence of glass.
Special Remarks on Reactivity	No additional remark.
Special Remarks on Corrosivity	No additional remark.
Polymerization	Not available.

Continued on Next Page

Section 11. Toxicological Information

Routes of Entry	Ingestion.
Toxicity to Animals	LD50: Not available LC50: Not available
Chronic Effects on Humans	The substance is toxic to blood, kidneys, liver Toxicity of the product to the reproductive system: Not available.
Other Toxic Effects on Humans	Very slightly to slightly dangerous in case of eye contact (irritant), of ingestion, of inhalation. Not dangerous in case of skin contact (non-corrosive for skin, non-irritant for skin, non-sensitizer for skin, non-permeator by skin).
Special Remarks on Toxicity to Animals	No additional remark.
Special Remarks on Chronic Effects on Humans	No additional remark.
Special Remarks on other Toxic Effects on Humans	No additional remark.

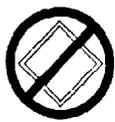
Section 12. Ecological Information

Ecotoxicity	Not available.
BOD5 and COD	Not available.
Products of Biodegradation	Some metallic oxides.
Toxicity of the Products of Biodegradation	The product itself and its products of degradation are not toxic.
Special Remarks on the Products of Biodegradation	No additional remark.

Section 13. Disposal Considerations

Waste Disposal	Recycle to process, if possible. Consult your local or regional authorities.
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Section 14. Transport Information

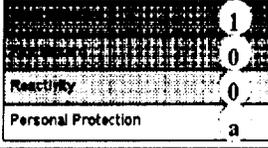
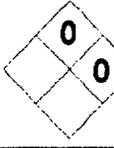
DOT Classification	Not a DOT controlled material (United States).
Identification	Not applicable (PIN and PG).
Special Provisions for Transport	Not applicable.
DOT (Pictograms)	

Section 15. Other Regulatory Information and Pictograms

Federal and State Regulations	The following product(s) is (are) listed on TSCA: Ferric subsulfate, Water
California Proposition 65 Warnings	WARNING: This product contains a chemical known to the State of California to cause cancer. Chemical ingredient(s) requiring this warning: NONE WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm. Chemical ingredient(s) requiring this warning: NONE
Other Regulations	OSHA. Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).

Continued on Next Page

Other Classifications	WHMIS (Canada) Not controlled under WHMIS (Canada).
	DSCL (EEC) Not controlled under DSCL (Europe).

HMIS (U.S.A.)		National Fire Protection Association (U.S.A.)	
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WHMIS (Canada) (Pictograms)	
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DSCL (Europe) (Pictograms)	
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TDG (Canada) (Pictograms)	
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ADR (Europe) (Pictograms)	
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Protective Equipment		Gloves.
		Lab coat.
		Safety glasses.

Section 16. Other Information

Catalog Number(s) FE107

References Not available.

Other Special Considerations No additional remark.

Validated by E. Brull on 9/26/97.	Verified by E. Brull. Printed 9/29/97.
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Emergency phone: (310)516-8000

Notice to Reader
All chemicals may pose unknown hazards and should be used with caution. This Material Safety Data Sheet (MSDS) applies only to the material as packaged. If this product is combined with other materials, deteriorates, or becomes contaminated, it may pose hazards not mentioned in this MSDS. It shall be the user's responsibility to develop proper methods of handling and personal protection based on the actual conditions of use. While this MSDS is based on technical data judged to be reliable, Spectrum Quality Products, Inc. assumes no responsibility for the completeness or accuracy of the information contained herein.

and titrate with 0.1 *N* potassium permanganate until a permanent pink color is produced. Each cc. of 0.1 *N* potassium permanganate corresponds to 15.19 mg. of FeSO₄. This assay is explained in the chapter on *Official Assays*.
Storage—Preserve the salt in well-closed containers.

Uses—This salt is more stable in air than the fully hydrated Ferrous Sulfate, and is more adaptable for making capsules, pills, and tablets.

Usual Dose—0.2 Gm. (approximately 3 grains).

Ferrous Sulfate Syrup U. S. P. Syrupus Ferri Sulfatis

[*Sp. Jarabe de Sulfato Ferroso*]

Ferrous Sulfate Syrup contains, in each 100 cc., not less than 3.75 Gm. and not more than 4.25 Gm. of FeSO₄·7H₂O.

	Metric	Alternative
Ferrous Sulfate	40 Gm.	1 oz. av. 147 gr.
Citric Acid	2.1 Gm.	31 gr.
Peppermint Spirit	2 cc.	31 min
Sucrose	825 Gm.	27 oz. av. 236 gr.
Distilled Water, a sufficient quantity,		
To make	1000 cc.	2 pints

Dissolve the ferrous sulfate, the citric acid, the peppermint spirit, and 200 Gm. of sucrose in 450 cc. of distilled water; and filter the solution until clear. Then dissolve the remainder of the sucrose in the clear filtrate, and add sufficient distilled water to make 1000 cc. Mix well and strain, if necessary, through a pledget of cotton.

Assay—Transfer 25 cc. of Ferrous Sulfate Syrup, accurately measured, to a 250-cc. Erlenmeyer flask. Add 15 cc. of diluted sulfuric acid and 100 cc. of water, and shake well. Titrate with 0.1 *N* ceric sulfate, using orthophenanthroline T.S. as the indicator. Each cc. of 0.1 *N* ceric sulfate is equivalent to 27.80 mg. of FeSO₄·7H₂O. This assay is explained in the chapter on *Official Assays*.
Storage—Preserve this Syrup in tight containers.

Uses—See *Ferrous Sulfate*.

Usual Dose—8 cc. (approximately 2 fluidrachms).

Ferrous Sulfate Tablets U. S. P. Tabellæ Ferri Sulfatis

[*Sp. Tabletæ de Sulfato Ferroso*]

Ferrous Sulfate Tablets contain not less than 95 per cent and not more than 110 per cent of the labeled amount of FeSO₄·7H₂O. An equivalent amount of exsiccated ferrous sulfate may be used in place of FeSO₄·7H₂O in preparing Ferrous Sulfate Tablets.

For tests for *Identification* and the *Weight variation* requirements, see the U. S. P.

Assay—Weigh a counted number of not less than 20 Ferrous Sulfate Tablets, and crush them well without appreciable loss. Weigh accurately in a beaker a portion of the crushed Tablets, equivalent to about 500 mg. of ferrous sulfate, and dissolve in a mixture of 20 cc. of diluted sulfuric acid and 80 cc. of freshly boiled and cooled water. Filter the solution rapidly as soon as all soluble ingredients in the tablets are dissolved, and wash the beaker and filter with small portions of a mixture of 20 cc. of diluted sulfuric acid and 80 cc. of water. Immediately titrate the combined filtrate and washings with 0.1 *N* ceric sulfate, using orthophenanthroline T.S. as the indicator. Each cc. of 0.1 *N* ceric sulfate is equivalent to 27.80 mg. of FeSO₄·7H₂O. This assay is explained in the chapter on *Official Assays*.
Storage—To minimize oxidation, these tablets should be kept in tight containers.

Usual Dose—0.3 Gm. (approximately 5 grains) of Ferrous Sulfate.

Unofficial Inorganic Iron Compounds

- Ferric Ammonium Sulfate, Ferric Alum—An official reagent.
- Ferric Chloride, Iron Perchlorate [FeCl₂·6H₂O]—An official reagent.
- Ferric Ferrocyanide, Fe₄[Fe(CN)₆]₃—Commonly called *Prussian blue*. A dark blue powder, insoluble in water. **Uses**: a pigment in paints, in inks, and in bluing. Formerly used in medicine as a tonic. **Dose**: 0.12 to 0.3 Gm. (2 to 5 grains).
- Ferric Ferrocyanide, Soluble, Soluble Iron Ferrocyanide [approximately KFe[Fe(CN)₆] + H₂O]—A blue powder, soluble in water, forming a colloidal solution.
- Ferric Fluoride [FeF₃ + H₂O]—White to slightly yellow, crystalline powder. Slightly soluble in water or in alcohol.
- Ferric Hydroxide, Antidotum Fuchsi, Hydrated Ferric Oxide—See *Magma of Ferric Hydroxide* (page 248).
- Ferric Nitrate [Fe(NO₃)₃]—Grayish white crystals; soluble in water.

Uses: a mordant in dyeing and in calico-printing; also a tonic and astringent.

Ferric Oxide, Saccharated N. F. VII—The following directions were given:

Dissolve 11 Gm. of monohydrated sodium carbonate in 150 cc. distilled water. Dilute 30 Gm. of ferric chloride solution with 150 cc. of distilled water and gradually add, with constant stirring, to the carbonate solution. Decant the supernatant liquid and wash the precipitate with distilled water until a portion of the washings, when diluted with 5 volumes of distilled water, give only a slight opalescence with silver nitrate T.S. Collect the precipitate on a cloth strainer, transfer the magma to a porcelain dish on a water bath, and add 50 Gm. of sucrose and a sufficient quantity (not more than 5 cc.) of a 15 per cent solution of sodium hydroxide to produce a clear solution. Evaporate the mixture to dryness upon a water bath and, if necessary, add sufficient powdered sucrose to make the product weigh 100 Gm. When so prepared it contains about 3 per cent of iron [Fe] corresponding to about 4.5 per cent of ferric oxide.

It occurs as a brown powder which is soluble in water but insoluble in alcohol. The iron in this preparation is non-ionic and it does not respond to some of the usual reactions for iron. **Uses**: a hematinic. **Dose**: 2 Gm. (30 grains) corresponding to 60 mg. of Fe.

Certain specially prepared solutions of saccharated ferric oxide may be administered intravenously, and are currently receiving trial for the treatment of refractory hypochromic anemias.

Ferric Phosphate [FePO₄·4H₂O]—A nearly white or slightly yellow, crystalline powder. Insoluble in water or in acetic acid; soluble in mineral acid. **Uses**: source of iron for the enrichment of foods.

Ferric Pyrophosphate [Fe₄(P₂O₇)₃·9H₂O]—Nearly white to slightly yellow, crystalline powder. Insoluble in water; soluble in mineral acids; also soluble when freshly prepared, in an excess of alkali citrate, forming green solutions.

Ferric Pyrophosphate, Soluble—This is a complex salt of sodium ferricitropyrophosphate. It is made by the process described for *Soluble Ferric Phosphate*, replacing the sodium phosphate with sodium pyrophosphate. It contains 11 to 13 per cent of iron. The iron in this phosphate is, like that in Soluble Ferric Phosphate, non-ionic. It occurs as bright green scales or as granules. It is freely soluble in water but insoluble in alcohol. **Uses**: a hematinic. **Dose**: 0.25 Gm. (4 grains).

Ferric Subsulfate [approximately Fe₄(SO₄)₅(OH)₂]—Yellow, somewhat hygroscopic powder, very slowly and usually incompletely soluble in water; insoluble in alcohol. **Uses**: a styptic, and a mordant in textile dyeing.

Ferric Sulfate [Fe₂(SO₄)₃]—Grayish white, very hygroscopic powder. Slowly soluble in water, sparingly soluble in alcohol. **Uses**: employed in dyeing, in the manufacture of Prussian blue and inks, and in water purification.

Ferrous Ammonium Sulfate—An official reagent.

Ferrous Bromide [FeBr₂]—A yellowish, deliquescent crystalline powder. Soluble in water. **Uses**: alterative and tonic. **Dose**: 0.06 to 0.2 Gm. (1 to 3 grains).

Ferrous Chloride [FeCl₂·H₂O]—Pale green, deliquescent crystals, or crystalline powder. Oxidizes on exposure to air. Soluble in 1 part water acidulated with hydrochloric acid; incompletely soluble in alcohol. **Uses**: astringent in gargles; also a mordant in printing fabrics and in dyeing.

Ferrous Iodide [FeI₂·4H₂O]—Almost black, very deliquescent masses. Decomposes rapidly in air with liberation of iodine. Freely soluble in cold water, decomposed by hot water; also soluble in alcohol. **Uses**: an alterative and tonic, generally given in pills or capsules.

Ferrous Phosphate [Fe₃(PO₄)₂·8H₂O]—On account of rapid oxidation in air the article of commerce contains basic ferric phosphate. A grayish blue powder. Insoluble in water, soluble in mineral acid. **Uses**: a hematinic; also used in coloring ceramics. **Dose**: 0.3 to 0.5 Gm. (5 to 8 grains).

Ferrous Sulfide [FeS]—An official reagent.

Inorganic Iron Specialties

Note—The following preparations, containing iron per se, or iron supplemented with vitamins and other substances, are used as hematinics and dietary supplements. The dose varies with the requirements of the individual.

- Aminoferin (J. T. Lloyd)—Liquid containing iron, aminoacetic acid, and thiamine hydrochloride in an oat menstruum.
- Arsenoferratose (Rare-Galen)—Elixir, each fluidounce containing sodium ferrialbuminate sufficient to furnish 235 mg. iron, and 0.9 mg. arsenic; tablets, each containing sodium ferrialbuminate to furnish 16 mg. iron, and 0.09 mg. arsenic.
- Ascoferrin (Dorsey)—Capsules, each containing 0.325 Gm. ferrous sulfate and 50 mg. ascorbic acid.
- B Ferrated (Upjohn)—Elixir, each fluidounce containing 1.3 Gm. ferrous sulfate with vitamin B complex supplement.
- Befolex (Central)—Tablets, each containing 19.4 mg. ferrous sulfate with folic acid and vitamin B complex factors.
- Beofer (Rexall)—Elixir or tablets, each fluidounce of the elixir containing 3 gr. ferrous sulfate, 2 mg. riboflavin, and 1 mg. thiamine hydrochloride; each tablet containing 3 gr. ferrous sulfate, 5 mg. nicotinic acid, 0.08 mg. pyridoxine hydrochloride, 0.6 mg. riboflavin, and 120 U. S. P. units vitamin B₁.
- Betacuron (Lakeside)—Liquid, each 30 cc. containing 274 mg. iron peptonate, 15.9 mg. copper gluconate, with vitamin B factors.
- Betaferrum (Hart Drug)—Elixir or tablets, each fluidounce of elixir containing 20 gr. ferrous sulfate and 3.6 mg. thiamine hydrochloride; each tablet containing 3 gr. exsiccated ferrous sulfate and 1.0 mg. thiamine hydrochloride.
- Betaron (Warren-Teed)—Syrup, each fluidounce containing 1 Gm. ferrous sulfate and 3 mg. thiamine hydrochloride.
- Biatron (National Drug)—Elixir, each fluidounce containing 4 gr. green iron and ammonium citrates, 5 per cent alcohol, 4 gr. calcium

JH

Dithymol Diiodide (Thymol Iodide).....	(C ₁₀ H ₁₂ O) ₂ I ₂	0-16
Dysprosium.....	Dy.....	550.03
Emetine.....	C ₁₅ H ₂₂ O ₂ N.....	162.5
" Hydrochloride, Anhydrous.....	C ₃₀ H ₄₄ O ₄ N ₂ ·2HCl.....	248.19
Epinephrine, Hydrated.....	C ₉ H ₁₃ O ₃ N + ½H ₂ O.....	569.31
Erbium.....	Er.....	192.12
Erythrol Tetranitrate.....	C ₄ H ₆ (NO ₃) ₄	167.7
Ether (Ethyl Oxide).....	(C ₂ H ₅) ₂ O.....	302.09
Ethyl Acetate.....	C ₂ H ₅ C ₂ H ₃ O ₂	74.08
" Carbamate.....	CO(OC ₂ H ₅)NH ₂	88.06
" Chloride.....	C ₂ H ₅ Cl.....	89.07
" Hydroxide (Ethyl Alcohol).....	C ₂ H ₅ OH.....	64.50
Ethylmorphine Hydrochloride.....	C ₁₉ H ₂₃ O ₃ NHCl + 2H ₂ O.....	46.05
" " Anhydrous.....	C ₁₉ H ₂₃ O ₃ NHCl.....	385.69
Ethyl Nitrite.....	C ₂ H ₅ NO ₂	349.66
" Oxide (Ether).....	(C ₂ H ₅) ₂ O.....	75.05
Eucaïne (Beta).....	C ₁₅ H ₂₁ O ₂ NHCl + H ₂ O.....	74.08
Eucalyptol (Cineol).....	C ₁₀ H ₁₈ O.....	301.66
Eugenol.....	C ₁₀ H ₁₂ O ₂	154.14
Europium.....	Eu.....	164.10
Ferric Acetate.....	Fe(C ₂ H ₃ O ₂) ₃	152.0
" Ammonium Sulphate.....	FeNH ₄ (SO ₄) ₂ + 12H ₂ O.....	232.91
" " Anhydrous.....	FeNH ₄ (SO ₄) ₂	482.21
" Chloride.....	FeCl ₃ + 6H ₂ O.....	266.02
" " Anhydrous.....	FeCl ₃	270.32
" Hydroxide.....	Fe(OH) ₃	162.22
" Hypophosphite.....	Fe(PH ₂ O ₂) ₃	106.86
" Nitrate.....	Fe(NO ₃) ₃	251.01
" Oxide.....	Fe ₂ O ₃	241.87
" Phosphate (normal, not U.S.P.).....	FePO ₄	159.68
" Pyrophosphate (normal, not U.S.P.).....	Fe ₄ (P ₂ O ₇) ₃	150.88
" Subsulphate (variable)		
" Sulphate (Tersulphate).....	Fe ₂ (SO ₄) ₃	745.60
Ferrous Bromide.....	FeBr ₂ + 6H ₂ O.....	399.89
" " Anhydrous.....	FeBr ₂	323.78
" Carbonate.....	FeCO ₃	215.68
" Iodide.....	FeI ₂	115.84
" Lactate.....	Fe(C ₃ H ₅ O ₃) ₂ + 3H ₂ O.....	309.68
" " Anhydrous.....	Fe(C ₃ H ₅ O ₃) ₂	287.97
" Oxide.....	FeO.....	233.92
" Sulphate.....	FeSO ₄ + 7H ₂ O.....	71.84
" " Anhydrous.....	FeSO ₄	278.02
" " Exsiccated (approximately).....	2FeSO ₄ + 3H ₂ O.....	151.91
" Sulphide.....	FeS.....	357.87
Ferrum.....	Fe.....	87.91
Fluorescein (Resorcinolphthalein).....	C ₂₀ H ₁₂ O ₆	55.84
Fluorine.....	F.....	332.10
		19.0

Assay—Dissolve about 1 Gm. of Soluble Ferric Phosphate, accurately weighed, in 25 ml. of water and 5 ml. of hydrochloric acid in a glass-stoppered flask; add 4 Gm. of potassium iodide, securely stopper the flask, and allow the mixture to stand 15 minutes; dilute with 50 ml. of water, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Perform a blank determination with the same quantities of the reagents and in the same manner and make any necessary correction. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 5.585 mg. of Fe.

Packaging and storage—Preserve Soluble Ferric Phosphate in well-closed, light-resistant containers.

CATEGORY—Hematinic.

USUAL DOSE—250 mg. (approximately 4 grains).

Ferric Subsulfate Solution

FERRIC SUBSULFATE SOLUTION

Monse's Solution

Basic Ferric Sulfate Solution

Ferric Subsulfate Solution is a water solution containing, in each 100 ml., basic ferric sulfate equivalent to not less than 20 Gm. and not more than 22 Gm. of Fe.

Ferrous Sulfate	1045 Gm.
Sulfuric Acid	55 ml.
Nitric Acid,	
Purified Water, each, a sufficient quantity,	
To make	1000 ml.

Add the sulfuric acid to 800 ml. of purified water in a suitable porcelain dish, and heat the mixture nearly to 100°; then add 75 ml. of nitric acid, and mix well. Divide the ferrous sulfate, coarsely powdered, into 4 approximately equal portions, and add these portions one at a time to the hot liquid, stirring after each addition until effervescence ceases. If, after the ferrous sulfate has dissolved, the solution has a black color, add nitric acid, a few drops at a time, with heating and stirring, until red fumes cease to be evolved. Boil the solution until it assumes a red color and is free from nitrate, as indicated by the test below, maintaining the volume at about 1000 ml. by the addition of purified water as needed. Cool, and add enough purified water to make the product measure 1000 ml.; filter, if necessary, until the product is clear.

NOTE: If exposed to low temperatures, crystallization may take place in the Solution. The crystals will redissolve upon warming the Solution.

Description—Ferric Subsulfate Solution is a reddish brown liquid, odorless or nearly so, with a sour, strongly astringent taste. Ferric Subsulfate Solution is acid to litmus, and it is affected by light. Its specific gravity is about 1.548.

A. INGREDIENT NAME:

FERRIC SUBSULFATE SOLUTION

B. Chemical Name:

C. Common Name:

Monsel's Solution, Basic Solution, Iron Hydroxide Sulfate

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specification)</i>	<i>(Result)</i>
Assay	20-22%	21.2%

E. Information about how the ingredient is supplied:

Reddish-Brown liquid, almost odorless, sour, strongly astringent taste, affected by light.

F. Information about recognition of the substance in foreign pharmacopeias:

NFXI

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Spitzer, M. and Chernys, A.E. Monsel's solution-induced artifact in the uterine cervix. *Am J Obstet Gynecol*, 1996; 175(5): 1204-1207.

Su, G. B. Clinical experience on efficacy of Monsel's solution. *Chung Hua Wai Ko Tsa Chih*, 1981; 19(11): 685-686.

Manca, D. P. Therapeutic use. Human/ Wound Healing. *Can Fam Physician*, 1997; 43: 1359.

H. Information about dosage forms used:

Solution

I. Information about strength:

20-22mg per 100ml
Undiluted

J. Information about route of administration:

Topically

K. Stability data:

L. Formulations:

Oxidizing ferrous sulfate with nitric acid
See file for compounding directions

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1168
54812

PRODUCT: FERRIC SUBSULFATE SOLUTION (PURIFIED)
RELEASE #: 104273 LOT # :B62908M10

GRADE: --
CODE:G09-21250/97

SPECIFICATIONS

RESULT

DESCRIPTION	SPECIFICATIONS	RESULT
1. DESCRIPTION	REDDISH-BROWN LIQUID	CONFORMS
2. Identification	To pass test	Passes test
3. Assay (Fe) [gm/100 ml]	20 - 22%	21.2%
4. Nitrate	Negative	Negative
5. Ferrous salts	Negative	Negative
6. Solubility	To pass test	Passes test

ATTENTION: TONY HATCHETT

Date :11/13/97

Prepared by : A. KASHWALA

10907

Approved by :

Our Order # 239573-1 Your PO # 54504

THE ABOVE TEST RESULTS HAVE BEEN OBTAINED BY OUR MANUFACTURER/SUPPLIER AND/OR IN OUR QUALITY CONTROL LABORATORY. THE DATA IS PROVIDED AT THE REQUEST OF AND FOR THE CONVENIENCE OF THE CUSTOMER AND DOES NOT RELIEVE THE CUSTOMER ITS RESPONSIBILITY TO VERIFY IT. THIS ANALYSIS IS NOT TO BE CONSTRUED AS A WARRANTY, EXPRESSED OR IMPLIED.

QUALITY CONTROL REPORT

CHEMICAL NAME.: (A) FERRIC SUBSULFATE (MONSEL'S SOLN)

MANUFACTURE LOT NO.: C63940C26

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

(REDDISH-BROWN LIQUID; ALMOST ODORLESS; SOUR, STRONGLY ASTRINGENT TASTE; AFFECTED BY LIGHT.

2) SOLUBILITY.:

MISCIBLE WITH WATER AND IN ALCOHOL; ACID TO LITMUS.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.: 1.548.

5) IDENTIFICATION.:

- A) FERROUS SALTS TEST GIVES NEGATIVE RESULTS.
- B) FERRIC SALTS TEST GIVES POSITIVE RESULTS.

PASSES.: _____

FAILS.: _____

COMMENTS.: NOTE - MAY CRYSTALLIZE OR SOLIDIFY AT LOW TEMPERATURES. K

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

MALLINCKRODT BAKER -- FERRIC SUBSULFATE SOLUTION - FERRIC SUBSULFATE SOLUTION
MATERIAL SAFETY DATA SHEET
NSN: 6505012078245
Manufacturer's CAGE: 70829
Part No. Indicator: A
Part Number/Trade Name: FERRIC SUBSULFATE SOLUTION

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General Information
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Item Name: FERRIC SUBSULFATE SOLUTION
Company's Name: MALLINCKRODT BAKER INC.
Company's Street: 222 RED SCHOOL LANE
Company's City: PHILLIPSBURG
Company's State: NJ
Company's Country: US
Company's Zip Code: 08865-2219
Company's Emerg Ph #: 908-859-2151/800-424-9300 (CHEMTREC)
Company's Info Ph #: 201-859-2151
Record No. For Safety Entry: 001
Tot Safety Entries This Stk#: 001
Status: SE
Date MSDS Prepared: 22AUG95
Safety Data Review Date: 30OCT96
Supply Item Manager: KX
MSDS Preparer's Name: UNKNOWN
MSDS Serial Number: BNVDB
Specification Number: NONE
Spec Type, Grade, Class: NOT APPLICABLE
Hazard Characteristic Code: J6
Unit Of Issue: BT
Unit Of Issue Container Qty: 500 ML
Type Of Container: STD COML PKG
Net Unit Weight: 3.2 LBS

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Ingredients/Identity Information
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Proprietary: NO
Ingredient: FERRIC SUBSULFATE
Ingredient Sequence Number: 01
Percent: 40-45
NIOSH (RTECS) Number: 1004946FS
CAS Number: 1310-45-8
OSHA PEL: NOT ESTABLISHED
ACGIH TLV: NOT ESTABLISHED
Other Recommended Limit: NONE RECOMMENDED

Proprietary: NO
Ingredient: SULFURIC ACID (SARA III)
Ingredient Sequence Number: 02
Percent:

Ferrous Sulphate, in clear crystals, <i>six hundred and seventy-five grammes</i>	675
Sulphuric Acid, <i>sixty-five grammes</i>	65
Nitric Acid,	
Distilled Water, each, <i>a sufficient quantity</i> ,	
To make <i>one thousand grammes</i>	1000

Add the Sulphuric Acid to *five hundred (500) cubic centimeters* Distilled Water in a capacious porcelain capsule, heat the mixture to nearly 100° C. (212° F.), then add *sixty-five (65) grammes* of Nitric Acid, and mix well. Divide the Ferrous Sulphate, coarsely powdered into four equal portions, and add these portions, one at a time to the hot liquid, stirring after each addition until effervescence ceases. When all of the Ferrous Sulphate is dissolved, add a few drops of Nitric Acid, and, if this causes a further evolution of red fumes, continue to add Nitric Acid, a few drops at a time, until it no longer causes red fumes to be evolved; then boil the Solution until it has acquired a ruby-red color and is free from nitrous odor. Lastly, add Distilled Water to make the product weigh *one thousand (1000) grammes*. Keep the product in well-stoppered bottles, in a moderate temperature place (not under 22° C. or 71.6° F.), protected from light.

This solution will sometimes crystallize, forming a semi-solid mass. When this occurs, the application of a gentle heat to the mass will restore the liquid condition.

NOTE.—Solution of Ferric Subsulphate is to be dispensed as such. Solution of Persulphate of Iron has been prescribed by the Pharmacopoeia.

A dark reddish-brown liquid, odorless or nearly so, of an astringent and styptic taste, and an acid reaction.

Specific gravity: about 1.550 at 15° C. (59° F.).

Miscible with water and alcohol, in all proportions, without decomposition. The diluted Solution yields a brownish-red precipitate with ammonium hydrochloride, a blue one with potassium ferrocyanide T.S., and a white one with hydrochloric acid, with barium chloride T.S.

On slowly mixing 2 volumes of the Solution with 1 volume of concentrated sulphuric acid, in a beaker, a semi-solid, white mass will separate (difference from *tersulphate*).

On adding a clear crystal of ferrous sulphate to a cooled mixture of 2 volumes of concentrated sulphuric acid and a diluted portion of the Solution, the crystal should not become brown, nor should there be a brown color developed around it (absence of *nitric acid*).

If to a small portion of the Solution, diluted with about 10 volumes of water, a few drops of freshly prepared potassium ferricyanide T.S. be added, a pure brown color should be produced, without a tinge of green or blue (absence of *ferrous salt*).

If 1.12 (1.1176) Gm. of the Solution be introduced into a glass bottle (having a capacity of about 100 Cc.), together with 15 Cc. of water and 2 Cc. of hydrochloric acid, and, after the addition of 1 Gm. of potassium iodide, the mixture be kept for half an hour at a temperature of 40° C.

with physiological salt solution and slowly administered intravenously.

Dosage Forms—Injection USP: 50 mg/5 ml, 250 mg/25 ml; for Injection USP: 50 mg.

Other Anticoagulant Antagonists

Tolonium Chloride [Toluidine Blue; Blutene (*Abbott*)] is 3-amino-7-(dimethylamino)-2-methylphenazathionium chloride [C₁₅H₁₆ClN₃S]. **Description and Solubility:** A dark-green powder. 1 Gm dissolves in about 26 ml of water,

yielding a blue to violet solution, and in about 175 ml of alcohol, yielding a blue solution. **Uses:** It precipitates heparin. It is used for the treatment of overdosage of heparin and for the treatment of certain hemorrhagic states, some of which, but not all, are associated with elevated blood heparinoid levels. The organs are stained blue and the urine becomes pale blue-green. Nausea, vomiting, burning sensation upon urination, and tenesmus may occur, but they may be avoided by adequate fluid intake. **Dose:** Oral, 200 to 300 mg daily for menorrhagia; intramuscular or slow intravenous, for heparin overdosage, 100 mg. **Veterinary Dose:** Oral, Dogs and Cats, 200 to 300 mg daily.

Hemostatics and Styptics

Many substances not especially related to the clotting mechanism are capable of promoting clotting. Upon contact with most surfaces, platelets disintegrate, thereby liberating a thromboplastin. Spongy and gauzy materials, which provide a large surface area, are thus used to arrest bleeding; absorbable sponges may be left permanently at the site of bleeding. Fibrin, fibrinogen, and thrombin are also potent hemostatics (see page 829). Astringents (see Chapter 43, page 768) also initiate clotting by precipitating proteins and by stabilizing platelets; ferric salts are mostly employed as styptics.

Alum—see page 769.

Cellulose, Oxidized—see page 1876.

Estrogens, Conjugated—see page 991.

Ferric Chloride—see page 772.

Fibrinogen—see page 830.

Fibrinogen with Antihemophilic Factor—see page 830.

Absorbable Gelatin Sponge USP

[Gelfoam (*Upjohn*)]

Absorbable Gelatin Sponge is gelatin in the form of a sterile, absorbable, water-insoluble sponge.

Description—A light, nearly white, nonelastic, tough, porous, hydrophilic solid. A 10-mm cube weighing approximately 9 mg will take up approximately 45 times its weight of well-agitated oxalated whole blood. It is stable in dry heat at 150° for 4 hours.

Solubility—Insoluble in water, but absorbable in body fluids; completely digested by a solution of pepsin.

Uses—Absorbable Gelatin Sponge is a hemostatic and coagulant used to control bleeding. It is moistened with thrombin solution or sterile normal saline and may then be left in place following the closure of a surgical incision. It is absorbed in from 4 to 6 weeks.

Human Antihemophilic Factor—see page 830.

Antihemophilic Human Plasma—see page 830.

Protamine Sulfate—see page 836.

Thrombin—see page 831.

Thromboplastin—see page 1376.

Tolonium Chloride—see this page.

Other Hemostatics and Styptics

Carbazochrome Salicylate [*Adrenosem (Massengill)*; *Adrestat (Organon)*]—An adrenochrome monosemicarbazone [3-hydroxy-1-methyl-5,6-indolinedione-5-semicarbazone] sodium salicylate complex [C₁₀H₁₂N₄O₃.C₇H₅NaO₃] occurring as a fine, orange-red, odorless powder with a sweetish saline taste. It is soluble in both alcohol and water. A 13% aqueous solution has a pH range of 6.7–7.3. **Uses:** Proposed for the systemic control of capillary bleeding of various types. Its clinical usefulness for this purpose is scientifically unjustified. **Dose:** Oral, 1 to 5 mg 4 times daily; intramuscular, 5 mg every 2 to 4 hours.

Ferric Subsulfate [approx. Fe₂O(SO₄)₅.H₂O]—Used and prepared only as a solution. Ferric Subsulfate Solution was official in NF XI. It is prepared by oxidizing ferrous sulfate with nitric acid. The solution contains 20–22 Gm Fe per 100 ml. It is reddish brown and has an astringent, sour taste. It is miscible with alcohol. **Uses:** An important styptic solution. The solution is less irritating than ferric sulfate because of the lesser amount of sulfuric acid present. It is occasionally used to control surface bleeding and as an astringent in a variety of skin disorders. It should not be used in vesicular, bulbous, or exudative dermatoses, because it may then cause permanent pigmentation of the skin.

Fibrin Foam Human—A dry artificial sponge of human fibrin, prepared by clotting with thrombin a foam of a solution of human fibrinogen. The clotted foam is dried from the frozen state and heated at 130° for 3 hours to sterilize. It appears as a fine, white sponge of firm texture. It is insoluble in water. **Uses:** A mechanical coagulant of blood in case of hemorrhage, especially in surgery of the brain, liver, kidneys, and other organs where ordinary methods of hemostasis are ineffective or inadvisable. This preparation is used by impregnating it with a freshly prepared solution of thrombin in normal saline solution and then applying the foam to the bleeding area. In time, the foam is absorbed.

Electrolytes

The concentration of several of the electrolytes in the plasma is critical for the proper functioning of the cells, especially those of the excitable tissues. For the normal plasma concentration of the principal electrolytes, see page 815. The proper balance of the several ions is complex; it depends not alone upon the concentration

in the extracellular fluid (of which plasma is one compartment) but also upon the intracellular concentration, the ratio across the cell membrane being an essential factor, and upon the ratio of one ion type to another. Thus, the plasma electrolyte concentrations provide only a crude clue to the electrolyte status of the patient.

It has been exposed to daylight for some time, yields a greenish or bluish color with potassium ferricyanide T.S. (presence of some ferrous salt).

Nitrate—Dilute 4 ml. of Ferric Chloride Tincture with 10 ml. of water, heat the solution by boiling and pour it into a mixture of 10 ml. of water and 10 ml. of ammonia T.S. Filter the mixture while hot, and wash the filter with the water until the total filtrate measures 30 ml. Mix the filtrate well and to 5 ml. add 2 drops of indigo carmine T.S. Mix this solution with 1 ml. of sulfuric acid: the blue color does not disappear within 1 minute.

Assay—Transfer 5 ml. of Ferric Chloride Tincture, accurately measured, to a flask of suitable capacity. Add about 20 ml. of water, 3 Gm. of potassium iodide, and 3 ml. of hydrochloric acid. Allow the solution to stand during 15 minutes; dilute it with 100 ml. of water, and then titrate with 0.1 N sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 N sodium thiosulfate is equivalent to 16.22 mg. of FeCl₃.

Alcohol content, page 404—Ferric Chloride Tincture contains from 58 to 64 per cent of C₂H₅OH.

Packaging and storage—Preserve Ferric Chloride Tincture in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

CATEGORY—Astringent; hematinic.
USUAL DOSE—0.6 ml.

Ferric Citrochloride Tincture

Ferric Citrochloride Tincture is a hydroalcoholic solution containing, in each 100 ml., ferric citrochloride equivalent to not less than 1.48 Gm. of Fe.

Ferric Chloride Solution.....	350 ml.
Sodium Citrate.....	450 Gm.
Alcohol.....	150 ml.
Water, a sufficient quantity,	
To make about.....	1000 ml.

Mix the ferric chloride solution with 150 ml. of water, dissolve the sodium citrate in the mixture with the aid of gentle heat, and add the alcohol. When the solution has become cold, add sufficient water to make the product measure 1000 ml. Set the Ferric Citrochloride Tincture aside in a cold place for a few days so that the excess of saline matter may separate, and then filter.

Assay—Transfer 5 ml. of Ferric Citrochloride Tincture, accurately measured, into an iodine flask, add 7 ml. of hydrochloric acid and 25 ml. of water, and heat on a water bath until clear. Cool to room temperature and add about 25 ml. of water and 3 Gm. of potassium iodide, and allow the mixture to stand for 15 minutes. Then remove the stopper and the sides of the flask with

additional 50 ml. of water and titrate the liberated iodine with 0.1 N sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 N sodium thiosulfate is equivalent to 5.585 mg. of Fe.

Alcohol content, page 404—Ferric Citrochloride Tincture contains from 13 to 15 per cent of C₂H₅OH.

Packaging and storage—Preserve Ferric Citrochloride Tincture in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

CATEGORY—Hematinic.
USUAL DOSE—0.5 ml.
One usual dose represents about 22 mg. of iron in the form of ferric citrochloride.

SOLUBLE FERRIC PHOSPHATE

Ferric Phosphate with Sodium Citrate

Soluble Ferric Phosphate is ferric phosphate rendered soluble by the presence of sodium citrate, and yields not less than 12 per cent and not more than 15 per cent of Fe.

Description—Soluble Ferric Phosphate occurs as thin, bright green, transparent scales, or as granules. It is without odor, and has an acid, slightly salty taste. Soluble Ferric Phosphate is stable in dry air when protected from light, but when unprotected, soon becomes discolored. A solution of Soluble Ferric Phosphate (1 in 10) is acid to litmus.

Solubility—Soluble Ferric Phosphate dissolves freely in water. It is insoluble in alcohol.

Identification—
A: To 10 ml. of a solution of Soluble Ferric Phosphate (1 in 100) add ammonia T.S., dropwise: the solution becomes reddish brown, but no precipitate forms.

B: Remove the iron from 10 ml. of a solution of Soluble Ferric Phosphate (1 in 10) by boiling it with an excess of sodium hydroxide T.S.; filter, and strongly acidify the filtrate with hydrochloric acid: a cooled portion of this liquid mixed with an equal volume of magnesia mixture T.S. and treated with a slight excess of ammonia T.S. produces an abundant, white, crystalline precipitate. This precipitate, after being washed, turns greenish yellow when treated with a few drops of silver nitrate T.S. (distinction from pyrophosphate).

Ammonium salts—Boil about 100 mg. of Soluble Ferric Phosphate with 5 ml. of sodium hydroxide T.S.: a reddish brown precipitate forms without the evolution of ammonia.

Lead—Dissolve 1 Gm. of Soluble Ferric Phosphate in 3 ml. of nitric acid (1 in 2) in a 100-ml. volumetric flask. Add sufficient water to make 100 ml., and mix well. A 10-ml. portion of this solution contains no more than 5 mcg. of lead (corresponding to not more than 50 parts per million) when treated according to the *Lead Limit Test*, page 414, using 10 ml. of ammonium citrate solution, 3 ml. of potassium cyanide solu-

tion, and 1 ml. of hydroxylamine hydrochloride solution.

Assay—Dissolve about 1 Gm. of Soluble Ferric Phosphate, accurately weighed, in 25 ml. of water and 5 ml. of hydrochloric acid in a glass-stoppered flask; add 4 Gm. of potassium iodide, securely stopper the flask, and allow the mixture to stand 15 minutes; dilute with 50 ml. of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate, using starch T.S. as the indicator. Perform a blank determination with the same quantities of the same reagents and in the same manner and make any necessary correction. Each ml. of 0.1 N sodium thiosulfate is equivalent to 5.585 mg. of Fe.

Packaging and storage—Preserve Soluble Ferric Phosphate in well-closed, light-resistant containers.

CATEGORY—Hematinic.
USUAL DOSE—250 mg.

FERRIC SUBSULFATE SOLUTION

Monsel's Solution; Basic Ferric Sulfate Solution

Ferric Sub sulfate Solution is a water solution containing, in each 100 ml., basic ferric sulfate equivalent to not less than 20 Gm. and not more than 22 Gm. of Fe.

NOTE: If exposed to low temperatures, crystallization may take place in the Solution. The crystals will redissolve upon warming the Solution.

Description—Ferric Sub sulfate Solution is a reddish brown liquid, odorless or nearly so, with a sour, strongly astringent taste. Ferric Sub sulfate Solution is acid to litmus, and it is affected by light. Its specific gravity is about 1.548.

Solubility—Ferric Sub sulfate Solution is miscible with water and with alcohol.

Identification—Separate portions of a dilution of Ferric Sub sulfate Solution (1 in 20) yield a brownish red precipitate with ammonia T.S., a blue precipitate with potassium ferrocyanide T.S., and a white precipitate, insoluble in hydrochloric acid, with barium chloride T.S.

Nitrate—Add a clear crystal of ferrous sulfate to a cooled mixture of equal volumes of sulfuric acid and a dilution of Ferric Sub sulfate Solution (1 in 10): the crystal does not become brown, nor does a brownish black color develop around it.

Ferrous salts—Add a few drops of freshly prepared potassium ferricyanide T.S. to 2 ml. of a dilution of Ferric Sub sulfate Solution (1 in 20): a brown color is produced and the solution remains free from even a transient green or greenish blue color.

Assay—Dilute about 10 ml. of Ferric Sub sulfate Solution, accurately measured, to exactly 100 ml. with water. Transfer 10 ml. of the dilution to a stoppered flask; add 5 ml. of hydrochloric acid and 3 Gm. of potassium iodide.

Stopper the flask, and allow the mixture to stand for 15 minutes; then dilute with 50 ml. of water, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 5.585 mg. of Fe.

Packaging and storage—Preserve Ferric Sub-sulfate Solution in tight, light-resistant containers, and in a moderately warm place (not under 22°).

CATEGORY—Astringent.

As a STYPTIC—Use Ferric Sub-sulfate Solution undiluted.

FERROUS CARBONATE PILLS

Chalybeate Pills
Blaud's Pills
Ferruginous Pills

Each Pill contains not less than 60 mg. of FeCO₃.

Ferrous Sulfate, in clear crystals....	16	Gm.
Potassium Carbonate.....	9.5	Gm.
Sucrose, finely powdered.....	4	Gm.
Tragacanth, finely powdered.....	1	Gm.
Althea, in very fine powder.....	1	Gm.
Glycerin,		
Purified Water, each, a sufficient quantity,		
To make 100 pills.		

Triturate the potassium carbonate in a mortar with a sufficient quantity (about 5 drops) of glycerin, add the ferrous sulfate and sucrose, previously triturated together to a uniform, fine powder, and mix the mass thoroughly until it assumes a greenish color. When the reaction is complete, incorporate the tragacanth and althea, and add purified water, if necessary, to obtain a mass of pilular consistency. Divide it into 100 pills.

Assay—Carefully pulverize 5 Ferrous Carbonate Pills in a mortar, and triturate with 20 ml. of diluted sulfuric acid until all carbonate is dissolved. Transfer completely the contents of the mortar to a beaker of about 800-ml. capacity, and add water to bring the total volume to approximately 300 ml. Add orthophenanthroline T.S., and titrate immediately with 0.1 *N* ceric sulfate, avoiding excessive stirring. Near the end of the titration tilt the beaker at an angle of 45° to facilitate the detection of the end point. Each ml. of 0.1 *N* ceric sulfate is equivalent to 11.59 mg. of FeCO₃.

Packaging and storage—Preserve Ferrous Carbonate Pills in well-closed containers.

CATEGORY—Hematinic.

USUAL DOSE—5 pills.

FERROUS IODIDE SYRUP

Ferrous Iodide Syrup contains, in each 100 ml., not less than 6.5 Gm. and not more than 7.5 Gm. of FeI₂, representing approximately 7 per cent of FeI₂, by weight.

Ferrous Iodide Syrup may be prepared as follows:

Iron, in the form of fine, bright wire.....	20	Gm.
Iodine.....	60	Gm.
Hypophosphorous Acid.....	5	ml.
Sucrose.....	850	Gm.
Purified Water, a sufficient quantity,		
To make.....	1000	ml.

NOTE: For the purpose of retarding discoloration, 1.3 Gm. of citric acid may replace the hypophosphorous acid in the above formula.

Place the iron in a flask having a capacity of about 500 ml., add the iodine and 200 ml. of purified water, and shake the mixture occasionally, checking the reaction, if necessary, by placing the flask in cold water. When the liquid has acquired a green color and has lost the odor of iodine, heat it to boiling, and dissolve 100 Gm. of sucrose in the hot liquid. Filter the solution at once into a flask graduated to 1000 ml. and containing the remainder of the sucrose, and rinse the flask containing the iron with 240 ml. of hot purified water in divided portions, passing the rinsings successively through the filter. Agitate the mixture until the sucrose is dissolved, warming if necessary, cool to 25°, and add the hypophosphorous acid and enough purified water to make the product measure 1000 ml. Mix and strain.

Description—Ferrous Iodide Syrup is a transparent, pale, yellowish green, syrupy liquid having a sweet, ferruginous taste and a slight acid reaction. Its specific gravity is about 1.2.

Identification—

A: Add a few drops of potassium ferrocyanide T.S. to 5 ml. of Ferrous Iodide Syrup; blue precipitate forms.

B: Mix 5 ml. of Ferrous Iodide Syrup with a few drops of starch T.S., and add 3 drops of chlorine T.S.: the liquid acquires a deep blue color.

Free iodine—To about 5 ml. of Ferrous Iodide Syrup add a few drops of starch T.S.: no blue color is produced.

Assay—Place exactly 10 ml. of Ferrous Iodide Syrup in a flask, dilute it with 30 ml. of water, add 50.0 ml. of 0.1 *N* silver nitrate, and 5 ml. of nitric acid, and heat on a water bath until a precipitate of silver iodide is greenish yellow. Cool, add 2 ml. of ferric ammonium sulfate T.S., and determine the residual silver nitrate by titration.

Dried Ferrous Sulphate (5064-n)

Ferrous Sulfate (USAN); Exsiccated Ferrous Sulphate; Ferrosi Sulfas Exsiccatus.

13463-43-9.

Pharmacopoeias. In Aust., Br., Int., and US.

Ferrous sulphate deprived of part of its water of crystallisation by drying at 40°. The USP specifies that it consists primarily of the monohydrate with varying amounts of the tetrahydrate. A greyish-white to buff-coloured powder. The BP specifies 86 to 90% of FeSO_4 ; the USP specifies 86 to 89% of FeSO_4 .

Slightly but almost completely soluble in freshly boiled and cooled water; practically insoluble in alcohol.

Ferrous sulphate is employed for iron-deficiency anaemia. It is given by mouth and the dried form is frequently used in solid dosage forms and the heptahydrate in liquid dosage forms. Usual doses of dried ferrous sulphate are up to 600 mg daily (equivalent to 180 to 195 mg of iron daily, this figure being somewhat variable depending on the purity and water content of the salt).

For discussion of iron-deficiency anaemia and its treatment, see p.747; for further discussion of iron and its dosage, see p.1368.

Ferrous sulphate oxidised with nitric and sulphuric acids yields ferric subsulphate solution, also known as Monsel's solution, which has been used as a haemostatic.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

BP 1993: Ferrous Sulphate Tablets; Paediatric Ferrous Sulphate Oral Solution; JCP 1973: Compound Ferrous Sulphate Tablets; USP 23: Ferrous Sulfate Oral Solution; Ferrous Sulfate Syrup; Ferrous Sulfate Tablets.

Proprietary Preparations

Aust.: Ferrograd C; Ferro-Gradumet; Infa-Tardyferon; Tardyferon; Austral.: Feritard; Ferro-Gradumet; Fespan; Slow-Fer; Belg.: Fer-In-Sol; Ferrograd; Ferro-Gradumet; Resoferon; Canad.: Fer-In-Sol; Ferro-Grad; Ferro-Grad-500; Novo-Ferrosulfa; Slow-Fer; Eire: Feospan; Fer-In-Sol; Ferrograd; Ferrograd C; Slow-Fer; Ger.: Ce-Ferro forte; Dreisäfer; Eisen-Diasporal; Eisendrangeestoff; Eryfer; Ferro 66 DL; Hamatopon; Haemoproject; Kendural C; Plastufer; Resoferix; Tardyferon; Taxofit Mineral Eisen; Vitafero; Ital.: Eryfer; Ferro-Grad; Ferro-Grad C; Neth.: Eryfer; Ferro-Gradumet; Liquifer; Plexafert; Resoferon; Norw.: Duroferon; Ferromax; Ferro-Retard; S.Afr.: Ferro-Grad; Fesofor; Spain: Ferro-Gradumet; Swed.: Duroferon; Switz.: Ferro-Gradumet; Résoféron; UK: Feospan; Ferrograd; Ferrograd C; Ironorm; Slow-Fe; USA: Feosol; Feratab; Fer-gen-sol; Fer-In-Sol; Fer-Iron; Ferro-Grad-500; Ferro-Gradumet; Ferospace; Ferralyn Lanacaps; Ferral-TD; Irospan; Mol-Iron; Slow-Fe.

Multi-ingredient preparations. Aust.: Aktiferin; Aktiferin compositum; Ferrograd-Fol; Kephaldoron; Tardyferon-Fol; Austral.: Fefol; Feritard-Fol; FGF Tabs; Canad.: Ferro-Fol; Iberet; Slow-Fe Folic; Eire: Fefol; Fefol-Vit; Ferrograd Folic; Fespan; Fofolite; Pregnavite Forte F; Slow-Fe Folic; Fr.: Ferro-Grad vitamin C; Ferro-Grad-500; Ionanthrol; Pilules Pink; Tardyferon; Tardyferon B; Ger.: Aktiferin; Aktiferin E F; Eryfer comp.; Ferro Cytofol; ferro sanol comp.; Ferro-Folgamma; Ferro-Fol-Fluor-Vicortrat; Ferro-Folsan; Ferro-Folsan plus; Ferrophort; Hamatopon F; Kendural-Fol-500; Kendural-Plus; Plastulen N; Tardyferon-Fol; Ital.: Cura; Ferro-Grad Folic; Vitamucin con Ferro; Norw.: Pregnifer; S.Afr.: Effe; Fefol; Fefolvit; Ferro-Folic; Foliglobin; Iberet; Laxicaps; Spain: Ferriwas B12 Fuerte; Ferosol; Iberet; Pildoras Ferrug Sunator; Tardyferon; Switz.: Actiferine; Actiferine-F; Ferro-Folic-500; gyno-Tardyferon; Infa-Tardyferon; Kendural; Résoféron fol B; Tardyferon; UK: Bidor; Dencyl; Ditemic; Fefol; Fefol Z; Fefol-Vit; Feospan Z; Feravol; Ferrograd Folic; Fesovit Z; Fesovint; Folicint; Fortespan; Irofol C; Ironorm; Ironplant; Pregnavite Forte F; Slow-Fe Folic; USA: Aqua Ban Plus; Ferro-Folic-500; Generet; Gerivites; Iberet; Iberet-Folic-500; Multibret Hematinic; Multibret-Folic; Reticulex†.

Ferrous Tartrate (5065-h)

Ferrosi Tartras.

$\text{C}_4\text{H}_4\text{FeO}_6 \cdot 2\frac{1}{2}\text{H}_2\text{O} = 249.0$.

CAS — 2944-65-2 (anhydrous ferrous tartrate).

Ferrous tartrate is employed for iron-deficiency anaemia. It is given by mouth in doses of up to 1 g daily (equivalent to up to 224 mg of iron daily).

For a discussion of iron-deficiency anaemia and its treatment, see p.747; for further discussion of iron and its dosage, see p.1368.

The symbol † denotes a preparation no longer actively marketed.

Folic Acid (7860-f)

Folic acid is a member of the vitamin B group which is essential for DNA synthesis and some amino-acid conversions and is involved in formate metabolism. Deficiency may result in megaloblastic anaemia. It is given by mouth for folate deficiency states, and also has a role in the prevention of neural tube defects. It should not be given for undiagnosed megaloblastic anaemia that may be due to vitamin B₁₂ deficiency, since it may mask continuing neurological degeneration.

Folic Acid (BAN, rINN).

Acidum Folium; Folacin; Folsynre; PGA; Pteroylglutamic Acid; Pteroylmonoglutamic Acid; N-[4-(2-Amino-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L-(+)-glutamic acid.

$\text{C}_{19}\text{H}_{19}\text{N}_7\text{O}_6 = 441.4$.

CAS — 59-30-3 (folic acid); 6484-89-5 (sodium folate).

Pharmacopoeias. In Aust., Belg., Br., Chin., Cz., Eur., Fr., Ger., Hung., Int., Jpn., Neth., Port., Swiss, and US.

The standards of Ph. Eur. apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

A yellow to orange brown, odourless or almost odourless crystalline powder.

BP solubilities are: practically insoluble in water and most organic solvents. USP solubilities are: very slightly soluble in water; insoluble in alcohol, acetone, chloroform, and ether. It readily dissolves in dilute solutions of alkali hydroxides and carbonates; soluble in hydrochloric acid and sulphuric acid. The USP injection has a pH of 8 to 11. Protect from light.

Stability in solution. A review of the compatibility and stability of components of total parenteral nutrition solutions when mixed in 1- or 3-litre flexible containers.¹ Folic acid has been reported to precipitate in some proprietary amino acid solutions and in the presence of high concentrations of calcium ions, but it appears to be stable and remain in solution provided the pH remains above 5. There have also been reports of folic acid being absorbed by the polyvinyl chloride container and administration set; however other studies have not substantiated such observations.

1. Allwood MC. Compatibility and stability of TPN mixtures in big bags. *J Clin Hosp Pharm* 1984; 9: 181-98.

Adverse Effects

Folic acid is generally well tolerated. Gastro-intestinal disturbances may occur. Hypersensitivity reactions have been reported rarely.

Precautions

Folic acid should never be given alone or in conjunction with inadequate amounts of vitamin B₁₂ for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B₁₂ deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the cord.

Caution is advised in patients who may have folate-dependent tumours.

Interactions. Folate status may be affected by a number of drugs and anticonvulsants, oral contraceptives, antituberculous drugs, alcohol, and folic acid antagonists including aminopterin, methotrexate, pyrimethamine, trimethoprim, and sulphonamides have all been said to produce folate deficiency states.¹ The authors of this review discuss possible mechanisms responsible for the folate deficiency and assess the clinical significance concluding that in some instances, such as during methotrexate or anticonvulsant therapy, replacement therapy with folic acid may become necessary in order to prevent megaloblastic anaemia developing.

Anticonvulsant-associated folate deficiency is discussed further under phenytoin, p.381.

1. Lambie DG, Johnson RH. Drugs and folate metabolism. *Drugs* 1985; 30: 145-55.

Pharmacokinetics

Folic acid is rapidly absorbed from normal diets, mainly from the proximal part of the small intestine, and is distributed in body tissues. The principal storage site is the liver; it is also actively concentrated in the cerebrospinal fluid. Dietary folates are stated to be less well absorbed than crystalline folic acid. The

naturally occurring folate polyglutamates are largely deconjugated and reduced prior to absorption but once absorbed, folic acid is reconverted via dihydrofolate to tetrahydrofolate and conjugated within the cells to form active polyglutamates. It is the 5-methyltetrahydrofolate which appears in the portal circulation, where it is extensively bound to plasma proteins.

There is an enterohepatic circulation for folate; about 4 to 5 µg is excreted in the urine daily. Administration of larger doses of folic acid leads to proportionately more of the vitamin being excreted in the urine. Folate is distributed into breast milk.

Human Requirements

Body stores of folate in healthy persons have been reported as being between 5 to 10 mg, but may be much higher. About 150 to 200 µg of folate a day is considered a suitable average intake for all healthy persons except women of child-bearing potential and pregnant women who require additional folic acid to protect against neural tube defects in their offspring (see below). Folate is present, chiefly combined with several L-(+)-glutamic acid moieties, in many foods, particularly liver, kidney, yeast, nuts, and leafy green vegetables. The vitamin is readily oxidised to unavailable forms and is easily destroyed during cooking.

In the United Kingdom dietary reference values (see p.1352) have been published for folate¹ and in the United States recommended daily allowances have been set.² Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. The special folate requirements to protect against neural tube defects are discussed below. In the UK the reference nutrient intake (RNI) for adult males and females is 200 µg daily and the estimated average requirement (EAR) is 150 µg daily. In the USA the allowances published have also recognised that diets containing lower amounts of folate maintain an adequate status and thus the allowance has been set at 200 µg for adult males and 180 µg for adult females.

Folate requirements are increased during pregnancy, apparently due to increased metabolic breakdown of folate rather than foetal transfer.³ An RNI of 300 µg daily has been suggested for pregnant women in the UK and an RDA of 400 µg daily in the USA. However, McPartlin and colleagues have suggested from a study in 6 pregnant women that these figures are too low, and that intakes of about 450 to 650 µg daily might be more appropriate.³ Interestingly, in the light of recent confirmation of the value of folate in preventing neural tube defects, it is now recommended that women planning a pregnancy receive a total daily intake of about 600 µg daily, before conception and during the first trimester, which would go some way towards supplying this increased amount.

A number of authorities in the UK and USA have advocated folic acid supplementation of bread or flour to increase the intake in women of childbearing age.^{4,7} However, there remains some debate over the appropriateness of such action, and the risks of masking underlying vitamin B₁₂ deficiency.^{8,5}

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 43*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs. Food and Nutrition Board. Commission on Life Sciences. National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989.
3. McPartlin J, et al. Accelerated folate breakdown in pregnancy. *Lancet* 1993; 341: 148-9.
4. DoH. *Folic acid and the prevention of neural tube defects: report from an expert advisory group*. London: Department of Health, 1992.
5. Committee on Genetics of the American Academy of Pediatrics. Folic acid for the prevention of neural tube defects. *Pediatrics* 1993; 92: 493-4.
6. Schorah CJ, Wild J. Fortified foods and folate intake in women of child-bearing age. *Lancet* 1993; 341: 1417.
7. Sutcliffe M, et al. Prevention of neural tube defects. *Lancet* 1994; 344: 1578.
8. Horton R. Fighting about folate. *Lancet* 1994; 344: 1696.
9. Wald NJ, Bower C. Folic acid, pernicious anaemia, and prevention of neural tube defects. *Lancet* 1994; 343: 307.

Uses and Administration

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidin nucleotides, and hence in the synthesis of DNA; it is also involved in some amino-acid conversions, an



TITLE: Monsel's solution-induced artifact in the uterine cervix.
AUTHOR: Spitzer M; Chernys AE
AUTHOR AFFILIATION: Department of Obstetrics and Gynecology, Queens Hospital Center, Jamaica, NY 11432, USA.
SOURCE: Am J Obstet Gynecol 1996 Nov;175(5):1204-7
NLM CIT. ID: 97097948
ABSTRACT: We documented and quantified Monsel's solution-related artifacts after cervical biopsies. All loop electrosurgical cone biopsy specimens over a 3-month period were reviewed for necrosis artifact of the surface epithelium. The degree of change was quantified and correlated with the antecedent use of Monsel's solution. Twenty-four cone biopsy specimens were evaluated. Three of the eight cone biopsy specimens obtained fewer than 10 days after the use of Monsel's solution showed definite changes. Between 10 and 18 days after the use of Monsel's solution, four of eight specimens showed change. After 18 days, none of eight specimens showed change. One specimen at 18 days showed focal changes that seemed to be related to the use of an unusually large amount of Monsel's solution, because the patient had had six biopsies within 2 days. The routine use of Monsel's solution may interfere with the ability to recognize and characterize disease process in cone biopsy specimens when the cone procedure is done within 3 weeks after the use of Monsel's solution.

9

MAIN MESH SUBJECTS: Cervix Uteri/DRUG EFFECTS/*PATHOLOGY
 Ferric Compounds/*ADVERSE EFFECTS
 Sulfates/*ADVERSE EFFECTS

ADDITIONAL MESH SUBJECTS: Artifacts
 Biopsy
 Female
 Human

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Ferric Compounds)
 0 (Sulfates)
 1310-45-8 (ferric subsulfate solution)



National Library of Medicine: IGM Full Record Screen



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TITLE: Stopping cervical bleeding.

AUTHOR: Manca DP

SOURCE: Can Fam Physician 1997 Dec;43:2121

NLM CIT. ID: 98088367

MAIN MESH SUBJECTS: *Cervix Uteri/INJURIES *
 Ferric Compounds/ADMINISTRATION & DOSAGE
 Hemorrhage/ETIOLOGY/THERAPY
 Hemostatics/ADMINISTRATION & DOSAGE
 Sulfates/ADMINISTRATION & DOSAGE

ADDITIONAL MESH SUBJECTS: Biopsy/ADVERSE EFFECTS
 Female
 Human
 Time Factors

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Eng

REGISTRY NUMBERS: 0 (Ferric Compounds)
 0 (Hemostatics)
 0 (Sulfates)
 1310-45-8 (ferric subsulfate solution)



Next Record	Order Documents	92,71 Other Years	Log off IGM
Details of Search	Return to Results	Return to Search Screen	Previous Record

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92-71 Other Years

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TITLE: ~~[Clinical experience on efficacy of Monsel's solution (author's transl)]~~ G

AUTHOR: Su GB

SOURCE: Chung Hua Wai Ko Tsa Chih 1981 Nov;19(11):685-6

NLM CIT. ID: 82185983

MAIN MESH SUBJECTS: Ferric Compounds/*THERAPEUTIC USE
Hemorrhage/*DRUG THERAPY
Hemostatics/*THERAPEUTIC USE
Iron/*THERAPEUTIC USE
Sulfates/*THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS: Adult
Aged
Case Report
English Abstract
Human
Male

PUBLICATION TYPES: JOURNAL ARTICLE

LANGUAGE: Chi

REGISTRY NUMBERS: 0 (Ferric Compounds)
0 (Hemostatics)
0 (Sulfates)
1310-45-8 (ferric subsulfate solution)
7439-89-6 (Iron)

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TITLE: Practice tips. Mole no more.
AUTHOR: Manca DP
SOURCE: Can Fam Physician 1997 Aug;43:1359
NLM CIT. ID: 97411097
MAIN MESH SUBJECTS: Ferric Compounds/***THERAPEUTIC USE**
 Hemostatics/***THERAPEUTIC USE**
 Nevus/***SURGERY**
 Skin Neoplasms/***SURGERY**
 Sulfates/***THERAPEUTIC USE**

ADDITIONAL MESH SUBJECTS: **Human**
Wound Healing

PUBLICATION TYPES: JOURNAL ARTICLE
LANGUAGE: Eng
REGISTRY NUMBERS: 0 (Ferric Compounds)
 0 (Hemostatics)
 0 (Sulfates)
 1310-45-8 (ferric subsulfate solution)



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Practice Tips

Donna P. Manca, MD, CCFP

Stopping cervical bleeding

Indications

This technique can be used for controlling cervical bleeding from a biopsied site. Occasionally, women present to me with bleeding after cervical biopsy or laser treatment for abnormal Pap smears. When they do present, bleeding is usually minimal and settles with watchful waiting. Occasionally a low-grade infection requires antibiotic treatment. On two occasions in my practice, bleeding was excessive and persistent after cervical biopsy or laser or loop excision. Examination of the cervix revealed an oozing injured site. I was able to stop the bleeding by applying Monsel's solution (20% ferric subsulfate) to the cervix.

This method is contraindicated when bleeding is from inside the os cervix or when excessive hemorrhaging requires further intervention.

Procedure

With ringed forceps and gauze, dab the cervix to identify the site of bleeding. Then, using ringed forceps with 2x2 gauze soaked in Monsel's solution, apply the solution directly to the bleeding site.

Discussion

The women I treated were discharged with no further complications or complaints.

Upon reviewing the literature, I found that Monsel's solution is often used in gynecologic oncology for bleeding from cervical and vaginal biopsies. One report¹ described a brownish vaginal discharge that appeared several days after the application of Monsel's when a vaginal pack soaked in Monsel's had been used. Monsel's solution is recommended over sutures after cold-knife conization in studies comparing these two methods of hemostasis.^{2,3} Monsel's solution also has been used in examining the vagina for papilloma virus and neoplasia.⁴

I could find no information in the literature on adverse effects for future Pap smears. Necrosis artifact could appear if cervical biopsy is performed within 3 weeks after application of Monsel's solution.¹ Monsel's solution appears to be a safe method for controlling cervical bleeding in this situation. Be aware that biopsies done within 3 weeks of using Monsel's solution can show artifacts. ♦

References

1. Barliff C. Preventing cervical bleeding with Monsel's solution. *Oncol Nurs Forum* 1992;19(4):664.
2. Gilbert L, Saunders NJ, Stringer R, Sharp F. Hemostasis and cold knife cone biopsy: a prospective, randomized trial comparing a suture versus non-suture technique. *Obstet Gynecol* 1989; 74(4):640-3.
3. Tantrakul S, Srisupundit S, Linasmita V, Bullangpoti S, Israngura N, Wilailak S, et al. A randomized study comparing suture with non-suture cold-knife conization. *J Obstet Gynecol* 1995;21(6):587-91.
4. Davis GD. Colposcopic examination of the vagina. *Obstet Gynecol Clin North Am* 1993;20(1):217-29.
5. Spitzer M, Chernys AE. Monsel's solution-induced artifact in the uterine cervix. *Am J Obstet Gynecol* 1996;175(5):1204-7.

We encourage readers to share some of their practice experience: the neat little tricks that solve difficult clinical situations. *Canadian Family Physician* will pay \$50 to authors upon publication of their practice tips.

Dr Manca, a Fellow of the College, practises family medicine in Edmonton.

A. INGREDIENT NAME:

FERRIC SULFATE HYDRATE

B. Chemical Name:

Diiron Trisulfate

C. Common Name:

Ferric Sulfate, Iron Persulfate, Iron Sesquisulfate, Iron Sulfate (2:3), Iron (3+) sulfate, Iron Tersulfate, Sulfuric Acid, Iron (3+) Salt (3:2)

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Purity: 73.0 min.

A solution responds to the test for ferric iron and sulfate.

E. Information about how the ingredient is supplied:

Grayish-white powder, or Rhombic or Rhombohedral crystals, very hygroscopic, commercial product usually contains about 20% water and is yellowish in color.

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Fuks, A. B., Holan, G., and Davis, J. M. Ferric sulfate versus dilute formocresol in pulpotomized primary molars: long-term follow up. *Pediatric Dentistry*, 1997; 19(5): 327-330.

Jeansonne, B. G., Boggs, W. S., and Lemon, R. R. Ferric sulfate hemostasis: effect on osseous wound healing. II. With curettage and irrigation. *Journal of Endodontics*, 1993; 19(4): 174-176.

Fei, A. L., Udin, r. d., and Johnson, R. A clinical study of ferric sulfate as a pulpotomy agent in primary teeth. *Pediatric Dentistry*, 1991; 13(6): 327-332.

Shaw, D. H., Krejci, R. F., and Kalkwarf, K. L. Gingival response to retraction by ferric sulfate. *Operative Dentistry*, 1983; 8(4): 142-147.

H. Information about dosage forms used:

Solution

I. Information about strength:

J. Information about route of administration:

K. Stability data:

Store at room temperature. Protect from light.

Stable

L. Formulations:

Ferrous Sulphate.....400gm

Sulphuric Acid.....78gm

Nitric Acid, Distilled water - a significant quantity.

See file for compounding formulation

M. Miscellaneous Information:

CERTIFICATE OF QUALITY

30-2267
53569

Product: FERRIC SULFATE, HYDRATE **A**
Grade: Reagent Grade
Lot: 2445A23

Appearance: Fine yellow crystalline powder **E**

Mol. Formula: $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$

Mol. Weight: 399.88 (anhydrous)

Description:

Assay:

	<u>Minimum</u>	<u>Maximum</u>	<u>Units</u>
0 Purity	<u>73.0</u>		%
Insolubles		0.02	%
Chloride (L=0.002)		<0.002	%
Ferrous Iron (L=0.02)		<0.02	%
Copper (L=0.005)		<0.005	%
Zinc (L=0.005)		<0.005	%
Nitrate (L=0.01)		<0.01	%
Non-precipitables (by NH3, L=0.1)		<0.1	%

Storage: Store at room temperature. Protect from moisture.

K

✓

10/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: FERRIC SULFATE HYDRATE

MANUFACTURE LOT NO.: 2036A41

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

GRAYISH-WHITE POWDER, OR RHOMBIC OR RHOMBOHEDRAL CRYSTALS; VERY HYGROSCOPIC; ~~COMMERCIAL PRODUCT USUALLY CONTAINS ABOUT 20% WATER AND IS YELLOWISH IN COLOR.~~

2) SOLUBILITY.:

SLOWLY SOLUBLE IN WATER, RAPIDLY SOLUBLE IN THE PRESENCE OF A TRACE OF FeSO_4 ; SPARINGLY SOLUBLE IN ALCOHOL; PRACTICALLY INSOLUBLE IN ACETONE, AND ETHYL ACETATE; HYDROLYZED SLOWLY IN AQUEOUS SOLUTIONS.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) A SOLUTION RESPONDS TO THE TEST FOR FERRIC IRON AND SULFATE.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____



Use your web browser's "Back" key to return to previous topic.

Ferric Sulfate Monohydrate

****** MATERIAL SAFETY DATA SHEET ******

Ferric Sulfate Monohydrate
45419

****** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ******

MSDS Name: Ferric Sulfate Monohydrate
Catalog Numbers:
S80013

Synonyms:

Diiron Trisulfate; Ferric Sulfate; Iron Persulfate; Iron Sesquisulfate; Iron Sulfate (2:3); Iron (3+) Sulfate; Sulfuric Acid, Iron

Company Identification: Fisher Scientific
1 Reagent Lane
Fairlawn, NJ 07410

For information, call: 201-796-7100
Emergency Number: 201-796-7100
For CHEMTREC assistance, call: 800-424-9300
For International CHEMTREC assistance, call: 703-527-3887

****** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ******

CAS#	Chemical Name	%	EINECS#
10028-22-5	Ferric sulfate, monohydrate	100	233-072-9

Hazard Symbols: XI
Risk Phrases: 36/37

****** SECTION 3 - HAZARDS IDENTIFICATION ******

EMERGENCY OVERVIEW

Appearance: yellow-gray.
Caution! May cause respiratory tract irritation. May cause liver and kidney damage. Causes severe digestive tract irritation with pain, nausea, vomiting and diarrhea. May corrode the digestive tract with hemorrhaging and possible shock.
Target Organs: None.

Potential Health Effects

- Eye:
May cause eye irritation.
- Skin:
May cause skin irritation.
- Ingestion:
May cause severe gastrointestinal tract irritation with nausea,

vomiting and possible burns. May cause liver and kidney damage.
 Inhalation:
 May cause respiratory tract irritation.
 Chronic:
 No information found.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
 Flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.
 Skin:
 Get medical aid if irritation develops or persists. Flush skin with plenty of soap and water.
 Ingestion:
 If victim is conscious and alert, give 2-4 cupfuls of milk or water. Never give anything by mouth to an unconscious person. Get medical aid immediately.
 Inhalation:
 Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.
 Notes to Physician:
 Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
 As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear.
 Extinguishing Media:
 Use alcohol foam, carbon dioxide, or water spray when fighting fires involving this material.
 Autoignition Temperature: Not applicable.
 Flash Point: Not applicable.
 NFPA Rating: Not published.
 Explosion Limits, Lower: Not available.
 Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.
 Spills/Leaks:
 Clean up spills immediately, observing precautions in the Protective Equipment section. Sweep up or absorb material, then place into a suitable clean, dry, closed container for disposal.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
 Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Use with adequate ventilation. Discard contaminated shoes.
 Storage:
 Store in a cool, dry place. Keep containers tightly closed.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:
 Use adequate ventilation to keep airborne concentrations low.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
Ferric sulfate, monohydrate	none listed	none listed	none listed

OSHA Vacated PELs:
 Ferric sulfate, monohydrate:
 No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

- Eyes: Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.
- Skin: Wear appropriate protective gloves to prevent skin exposure.
- Clothing: Wear appropriate protective clothing to prevent skin exposure.
- Respirators: A respiratory protection program that meets OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions warrant a respirator's use.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State: Solid
 Appearance: yellow-gray
 Odor: Odorless.
 pH: Not available.
 Vapor Pressure: Negligible.
 Vapor Density: Not available.
 Evaporation Rate: Negligible.
 Viscosity: Not available.
 Boiling Point: Not applicable.
 Freezing/Melting Point: Decomposes.
 Decomposition Temperature: 480 deg C
 Solubility: Soluble in water.
 Specific Gravity/Density: 3.097
 Molecular Formula: Fe2(SO4)3.H2O
 Molecular Weight: 399.8668

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:
~~Stable under normal temperatures and pressures.~~
 Conditions to Avoid:
 Incompatible materials.
 Incompatibilities with Other Materials:
 Corrosive to metals.
 Hazardous Decomposition Products:
 Sulfur oxides (SOx), including sulfur oxide and sulfur dioxide.
 Hazardous Polymerization: Will not occur.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
 CAS# 10028-22-5: NO8505000
 LD50/LC50:
 Not available.
 Carcinogenicity:
 Ferric sulfate, monohydrate -
 Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.
 Epidemiology:
 No data available.
 Other Studies:
 No data available.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Environmental Fate:
 Not available.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
 RCRA D-Series Maximum Concentration of Contaminants: Not listed.
 RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
 RCRA F-Series: Not listed.
 RCRA P-Series: Not listed.
 RCRA U-Series: Not listed.
 Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
 Shipping Name: CORROSIVE SOLID, ACIDIC, INORGANIC, N.O.S.
 (SULFURIC ACID)
 Hazard Class: 8
 UN Number: UN3260
 Packing Group: II

IMO
 No information available.

IATA
 No information available.

RID/ADR
 No information available.

Canadian TDG
 No information available.

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA
 CAS# 10028-22-5 is listed on the TSCA inventory.
 Health & Safety Reporting List
 None of the chemicals are on the Health & Safety Reporting List.
 Chemical Test Rules
 None of the chemicals in this product are under a Chemical Test Rule.
 Section 12b
 None of the chemicals are listed under TSCA Section 12b.
 TSCA Significant New Use Rule
 None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)
 final RQ = 1000 pounds (454 kg)
 Section 302 (TPQ)
 None of the chemicals in this product have a TPQ.
 Section 313
 No chemicals are reportable under Section 313.

Clean Air Act:

This material does not contain any hazardous air pollutants.
 This material does not contain any Class 1 Ozone depletors.
 This material does not contain any Class 2 Ozone depletors.

Clean Water Act:

CAS# 10028-22-5 is listed as a Hazardous Substance under the CWA.
 None of the chemicals in this product are listed as Priority
 Pollutants under the CWA.
 None of the chemicals in this product are listed as Toxic Pollutants
 under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous
 by OSHA.

STATE

Ferric sulfate, monohydrate can be found on the following state right
 to know lists: New Jersey, Pennsylvania, Massachusetts.

California No Significant Risk Level:

None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: XI

Risk Phrases:

R 36/37 Irritating to eyes and respiratory system.

Safety Phrases:

WGK (Water Danger/Protection)

CAS# 10028-22-5: 1

Canada

CAS# 10028-22-5 is listed on Canada's DSL/NDSL List.

WHMIS: Not available.

CAS# 10028-22-5 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

CAS# 10028-22-5: . OEL-DENMARK:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-FINLAND:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-THE NETHERLANDS:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-SWITZERLAND:TWA 1 mg(Fe)/m3 JANUARY 1993. OEL-UNITED KINGDOM:TWA 1 mg(Fe)/m3;STEL 2 mg(Fe)/m3 JANUARY 1993. OEL IN BULGARIA, COLOMBIA, JORDAN, KOREA check ACGIH TLV. OEL IN NEW ZEALAND, SINGAPORE, VIETNAM check ACGI TLV

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 6/28/1995 Revision #3 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

ite, in clear crystals, *six hundred and animes*..... 675 Gm.
sixty-five grammes..... 65 Gm.

r, each, a sufficient quantity,

To make one thousand grammes.... 1000 Gm.

ric Acid to five hundred (500) cubic centimeters in a capacious porcelain capsule, heat the mixture to 212° F.), then add sixty-five (65) grammes of Ferrous Sulphate, coarsely powdered in four equal portions, and add these portions, one at a time, stirring after each addition until effervescence ceases. When the Ferrous Sulphate is dissolved, add a few drops of Nitric Acid, if this causes a further evolution of red fumes; then add a few drops of Nitric Acid, a few drops at a time, until it no longer causes red fumes to be evolved; then boil the Solution until it assumes a reddish-brown color and is free from nitrous odor. Lastly, add enough Distilled Water to make the product weigh one thousand (1000) grammes. Filter, if necessary. The product should be a dark reddish-brown liquid, almost odorless, having an acid, strongly op-tic taste, and an acid reaction. Specific gravity: about 1.320 at 15° C. (59° F.). Miscible with water and alcohol, in all proportions, without decomposition. The diluted Solution yields a brownish-red precipitate with ammonia water, a blue one with potassium ferrocyanide T.S., and a white one, insoluble in hydrochloric acid, with barium chloride T.S. On slowly mixing 2 volumes of the Solution with 1 volume of concentrated sulphuric acid, in a beaker, no solid, white mass will separate on standing (difference from subsulphate). On adding a clear crystal of ferrous sulphate to a cooled mixture of equal volumes of concentrated sulphuric acid and a moderately diluted portion of the Solution, the crystal should not become brown, nor should there be a brownish-black color developed around it (absence of nitric acid). If to a small portion of the Solution, diluted with about 10 volumes of water, a few drops of freshly prepared potassium ferricyanide T.S. be added, a pure brown color should be produced, without a tinge of green or greenish-blue (absence of ferrous salt).

on of Ferric Subsulphate is to be dispensed as such, when the Ferric Sulphate of Iron has been prescribed by the physician.

ish-brown liquid, odorless or nearly so, of an acid reaction. Specific gravity: about 1.550 at 15° C. (59° F.).

Miscible with water and alcohol, in all proportions, without decomposition. The diluted Solution yields a brownish-red precipitate with ammonia water, a blue one with potassium ferrocyanide T.S., and a white one, insoluble in hydrochloric acid, with barium chloride T.S.

On slowly mixing 2 volumes of the Solution with 1 volume of concentrated sulphuric acid, in a beaker, a semi-solid, white mass will separate on standing (difference from subsulphate).

On adding a clear crystal of ferrous sulphate to a cooled mixture of equal volumes of concentrated sulphuric acid and a moderately diluted portion of the Solution, the crystal should not become brown, nor should there be a brownish-black color developed around it (absence of nitric acid).

If to a small portion of the Solution, diluted with about 10 volumes of water, a few drops of freshly prepared potassium ferricyanide T.S. be added, a pure brown color should be produced, without a tinge of green or greenish-blue (absence of ferrous salt).

176) Gm. of the Solution be introduced into a glass capsule of a capacity of about 100 Cc., together with 15 Cc. of hydrochloric acid, and, after the addition of 1 Gm. of potassium dichromate, the mixture be kept for half an hour at a temperature of 50° C. (122° F.), then cooled, and mixed with a few drops of starch T.S., it should require about 27.2 Cc. of decinormal sodium hyposulphite V.S. to discharge the blue or greenish color of the liquid (each Cc. of the volumetric solution indicating 0.5 per cent. of metallic iron).

F.), then cooled, and mixed with a few drops of starch T.S., it should require about 27.2 Cc. of decinormal sodium hyposulphite V.S. to discharge the blue or greenish color of the liquid (each Cc. of the volumetric solution indicating 0.5 per cent. of metallic iron).

LIQUOR FERRI TERSULPHATIS.
 SOLUTION OF FERRIC SULPHATE.

An aqueous solution of normal Ferric Sulphate [Fe₂(SO₄)₃ = 399.22], containing about 28.7 per cent. of the salt, and corresponding to about 10 per cent. of metallic iron.

Ferrous Sulphate, in clear crystals, *four hundred grammes* 400 Gm.
 Sulphuric Acid, *seventy-eight grammes*..... 78 Gm.
 Nitric Acid,
 Distilled Water, each, a sufficient quantity,

To make one thousand grammes.... 1000 Gm.

Add the Sulphuric Acid to two hundred (200) cubic centimeters of Distilled Water in a capacious porcelain capsule, heat the mixture to nearly 100° C. (212° F.), then add fifty-five (55) grammes of Nitric Acid, and mix well. Divide the Ferrous Sulphate, coarsely powdered, into four equal portions, and add these portions, one at a time, to the hot liquid, stirring after each addition until effervescence ceases. When all of the Ferrous Sulphate is dissolved, add a few drops of Nitric Acid, and, if this causes a further evolution of red fumes, continue to add Nitric Acid, a few drops at a time, until it no longer causes red fumes to be evolved; then boil the Solution until it assumes a reddish-brown color and is free from nitrous odor. Lastly, add enough Distilled Water to make the product weigh one thousand (1000) grammes. Filter, if necessary.

A dark reddish-brown liquid, almost odorless, having an acid, strongly op-tic taste, and an acid reaction.

Specific gravity: about 1.320 at 15° C. (59° F.).

Miscible with water and alcohol, in all proportions, without decomposition. The diluted Solution yields a brownish-red precipitate with ammonia water, a blue one with potassium ferrocyanide T.S., and a white one, insoluble in hydrochloric acid, with barium chloride T.S.

On slowly mixing 2 volumes of the Solution with 1 volume of concentrated sulphuric acid, in a beaker, no solid, white mass will separate on standing (difference from subsulphate).

On adding a clear crystal of ferrous sulphate to a cooled mixture of equal volumes of concentrated sulphuric acid and a moderately diluted portion of the Solution, the crystal should not become brown, nor should there be a brownish-black color developed around it (absence of nitric acid).

If to a small portion of the Solution, diluted with about 10 volumes of water, a few drops of freshly prepared potassium ferricyanide T.S. be added, a pure brown color should be produced, without a tinge of green or greenish-blue (absence of ferrous salt).

Dithymol Diiodide (Thymol Iodide)	$(C_{10}H_{12}O)_2I_2$	0-16
Dysprosium	Dy	550.03
Emetine	$C_{15}H_{22}O_2N$	162.5
“ Hydrochloride, Anhydrous	$C_{30}H_{44}O_4N_2 \cdot 2HCl$	248.19
Epinephrine, Hydrated	$C_9H_{13}O_3N + \frac{1}{2}H_2O$	569.31
Erbium	Er	192.12
Erythrol Tetranitrate	$C_4H_6(NO_3)_4$	167.7
Ether (Ethyl Oxide)	$(C_2H_5)_2O$	302.09
Ethyl Acetate	$C_2H_5C_2H_3O_2$	74.08
“ Carbamate	$CO(OC_2H_5)NH_2$	88.06
“ Chloride	C_2H_5Cl	89.07
“ Hydroxide (Ethyl Alcohol)	C_2H_5OH	64.50
Ethylmorphine Hydrochloride	$C_{19}H_{23}O_3NHCl + 2H_2O$	46.05
“ “ Anhydrous	$C_{19}H_{23}O_3NHCl$	385.69
Ethyl Nitrite	$C_2H_5NO_2$	349.66
“ Oxide (Ether)	$(C_2H_5)_2O$	75.05
Eucaine (Beta)	$C_{15}H_{21}O_2NHCl + H_2O$	74.08
Eucalyptol (Cineol)	$C_{10}H_{18}O$	301.66
Eugenol	$C_{10}H_{12}O_2$	154.14
Europium	Eu	164.10
Ferric Acetate	$Fe(C_2H_3O_2)_3$	152.0
“ Ammonium Sulphate	$FeNH_4(SO_4)_2 + 12H_2O$	232.91
“ “ Anhydrous	$FeNH_4(SO_4)_2$	482.21
“ Chloride	$FeCl_3 + 6H_2O$	266.02
“ “ Anhydrous	$FeCl_3$	270.32
“ Hydroxide	$Fe(OH)_3$	162.22
“ Hypophosphite	$Fe(PH_2O_2)_3$	106.86
“ Nitrate	$Fe(NO_3)_3$	251.01
“ Oxide	Fe_2O_3	241.87
“ Phosphate (normal, not U.S.P.)	$FePO_4$	159.68
“ Pyrophosphate (normal, not U.S.P.)	$Fe_4(P_2O_7)_3$	150.88
“ Subsulphate (variable)		745.60
“ Sulphate (Tersulphate)	$Fe_2(SO_4)_3$	399.89
Ferrous Bromide	$FeBr_2 + 6H_2O$	323.78
“ “ Anhydrous	$FeBr_2$	215.68
“ Carbonate	$FeCO_3$	115.84
“ Iodide	FeI_2	309.68
“ Lactate	$Fe(C_3H_5O_3)_2 + 3H_2O$	287.97
“ “ Anhydrous	$Fe(C_3H_5O_3)_2$	233.92
“ Oxide	FeO	71.84
“ Sulphate	$FeSO_4 + 7H_2O$	278.02
“ “ Anhydrous	$FeSO_4$	151.91
“ “ Exsiccated (approximately)	$.2FeSO_4 + 3H_2O$	357.87
“ Sulphide	FeS	87.91
Ferrum	Fe	55.84
Fluorescein (Resorcinolphthalein)	$C_{20}H_{12}O_5$	332.10
Fluorine	F	19.0

Practically nontoxic. A mild local irritant. Large doses orally can cause diarrhea.

VET USE: Locally as styptic. Diluted orally in G.I. tract hemorrhages.

Ferric Sulfate. Ferric persulfate; ferric sesquisulfate; ferric tersulfate. $\text{Fe}_2(\text{SO}_4)_3$; mol wt 399.88. Fe 27.93%, O 48.01%, S 24.06%. Prepn: *Gmelin's Handb. anorg. Chem.*, System no. 59 (Iron), part B, pp 439-462 (1932).

Grayish-white powder, or rhombic or rhombohedral crystals. Very hygroscopic. Commercial product usually contains about 20% water and is yellowish in color. d_{20}^{25} 3.097. Slowly sol in water, rapidly sol in the presence of a trace of FeSO_4 ; sparingly sol in alcohol; practically insol in acetone, ethyl acetate. Hydrolyzed slowly in aq soln. *Keep well closed and protected from light.* LD s.c. in frogs: 13 g/kg.

USE: In prepn of iron alums, other iron salts and pigments; as coagulant in water purification and sewage treatment; in etching aluminum; in pickling stainless steel and copper; as mordant in textile dyeing and calico printing; in soil conditioners; as polymerization catalyst.

Ferric Tannate. Ferric gallotannate. Variable composition. Contains 8-10% Fe, 70-80% tannin.

Bluish-black powder. Insoluble in water; sol in dil mineral acids.

USE: In inks.

Ferric Thiocyanate. Ferric sulfocyanate; ferric sulfocyanide. $\text{Fe}(\text{SCN})_3$; mol wt 230.08. $\text{C}_3\text{FeN}_3\text{S}_3$; C 15.66%, Fe 24.27%, N 18.26%, S 41.81%. Prepn: *Gmelin's Handb. anorg. Chem.*, System no. 59 (Iron), part B, pp 747-761 (1932); Uri, *J. Chem. Soc.* 1947, 336.

Sesquihydrate, $\text{Fe}(\text{SCN})_3 \cdot 1\frac{1}{2}\text{H}_2\text{O}$, red, deliquescent crystals. Dec on heating. Soluble in water, alcohol, ether, acetone, pyridine, ethyl acetate; practically insol in CHCl_3 , CCl_4 , CS_2 , toluene. *Keep well closed.*

USE: Analytical reagent.

Ferrite. Ferrosphenel. A crystalline, usually man-made material, having a spinel structure and consisting essentially of ferric oxide and at least one other metallic oxide which is usually, although not always, divalent in nature. When molded into compressed bodies, the material is characterized by high magnetic permeability. Typified composition: Fe_2O_3 67-70%; ZnO 10-10.5%; MnO_2 20-22.5%; CuO 0.1-10%; Co_2O_3 0.1%. Ferrites are prepd by ceramic techniques. The oxides or carbonates are milled in steel ball mills, and the mixture of very fine particles is dried and fired in order to obtain a homogeneous end product: Hilpert, *Ber.* 42, 2248 (1909). Examples of modern techniques: Simpkins, U.S. pat. 2,723,238 (1955 to Radio Corp. of America); Harvey, U.S. pat. 2,723,239 (1955 to Radio Corp. of America). Books: Snoek, *New Developments in Ferromagnetic Materials* (Elsevier, New York, 1947); Smit, Wijn, *Ferrites* (John Wiley & Sons, Inc., New York, 1959); Soehov, *Theory and Application of Ferrites* (Prentice Hall, 1960); Standley, *Oxide Magnetic Materials* (Clarendon Press, Oxford, 1962). *Reviews with bibliographies:* Gorter, *Proc. I.R.E.* 43, 1945-1973 (1955); Fresh, "Methods of Preparation and Crystal Chemistry of Ferrites," *ibid.* 44, 1303-1311 (1956); Brailsford, *Magnetic Materials* (3rd ed, John Wiley & Sons, Inc., 1960), pp 160-181; Hogan, *Sci. Am.* 202, 92-104 (1960); Economos, Kirk-Othmer's *Encyclopedia of Chemical Technology* vol. 8 (2nd ed, Interscience, 1965), pp 881-901.

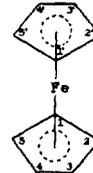
USE: Radio and television coil cores; slug tuners, loopstick antennas. *Human Toxicity:* The dust can cause pulmonary irritation. *See also* specific metals.

Ferritin. A crystallizable protein contg 20-24% iron and 1.2-2% phosphorus. Forms a large part of the storage iron in spleen, intestinal mucosa, and liver. Isolated from horse spleen. *Review:* Kleinwachter, *Chem. Listy* 55, 234 (1961).

Ferroakermanite. $2\text{CaO} \cdot \text{FeO} \cdot 2\text{SiO}_2$ —calcium iron silicate.

Ferrocene. *Dicyclopentadienyliron*; *biscyclopentadienyliron*. $\text{C}_{10}\text{H}_{10}\text{Fe}$; mol wt 186.03. C 64.56%, H 5.42%, Fe 30.02%. Prepns: Kealy and Pauson, *Nature* 168, 1039 (1951); Pauson, U.S. pat. 2,680,756 (1954 to Du Pont); Miller *et al.*, *J. Chem. Soc.* 1952, 632; Anzilotti and Weinmayr, U.S. pat. 2,791,597 (1957 to Du Pont). Other preps: Wilkinson, *Org. Syn.* 36, 31, 34 (1956); Pruett, Morehouse, *Advances in Chemistry Series* 23, 368-371 (1959); Wilkinson, *Org. Syn.*, coll. vol. IV, 473 (1963); Cordes, *Fr. pat.* 1,341,880

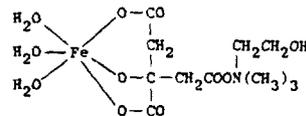
(1963 to BASE); *C.A.* 60, 6873a. Structure studies: Wilkinson *et al.*, *J. Am. Chem. Soc.* 74, 2125 (1952); Seibold and Sutton, *J. Chem. Phys.* 23, 1967 (1955). *Review on ferrocene reactions:* Rausch *et al.*, *J. Chem. Ed.* 34, 268 (1957). Book: Rosenblum, *Chemistry of the Iron Group Metallocenes* (John Wiley, New York), 1965.



Orange needles from methanol or ethanol; odor of camphor. mp 173-174°. Sublimes above 100°. Volatile in steam. Practically insol in water, 10% NaOH, and concd boiling HCl. Soluble in alcohol, ether, benzene. Also dissolves in dil nitric and concd sulfuric acids forming a deep red soln with blue fluorescence. The molecule is diamagnetic and the dipole moment is effectively zero.

USE: Antiknock additive for gasoline; catalyst. *Human Toxicity:* No specific data. Animal feeding expts show almost complete absence of toxicity.

Ferrocenolinate. [*Hydrogen citrato(3-)*]triferriciron, *choline salt*; iron choline citrate; Chelafer; Chel-Iron; Ferrolip. $\text{C}_{11}\text{H}_{24}\text{FeNO}_{11}$; mol wt 402.17. C 32.85%, H 6.01%, Fe 13.89%, N 3.48%, O 43.76%. Prepd by interaction of equimolar quantities of choline dihydrogen citrate and freshly prepd $\text{Fe}(\text{OH})_3$ or FeCO_3 ; Bandelin, U.S. pat. 2,575,611 (1951 to Flint Eaton & Co.); by treatment of a freshly prepd soln of ferric citrate with an equimolar amount of choline: Chakrabarti, Sen, *Chemistry & Industry (London)* 1961, 1407.



Greenish-brown, reddish-brown or brown amorphous solid with glistening surface upon fracture. Freely sol in water, yielding stable solns; sol in acids, alkalis. One gram of pharmaceutical grade is equivalent to 120 mg of elemental iron and 360 mg of choline base.

Note: Other combinations of iron, choline and citric acid have been prepd for pharmaceutical use. A 1:2:2 chelate, $\text{C}_{22}\text{H}_{36}\text{FeN}_2\text{O}_{16}$, was reported by Chakrabarti and Sen, *loc. cit.*, and a 2:3:3 chelate, $\text{C}_{33}\text{H}_{57}\text{Fe}_2\text{N}_3\text{O}_{24}$, by Rosenfelder, U.S. pat. 2,865,938 (1958 to H. Rosenstein).

MED USE: Hematinic in iron deficiency anemia.

Ferrodolomite. $\text{CaFe}(\text{CO}_3)_2$ —calcium iron carbonate.

Ferroglycine Sulfate. Ferroglycine sulfate complex; ferrous sulfate glycine complex; ferrous aminoacetosulfate; iron sulfate-glycine complex; glycine-ferrous sulfate complex; Plesmet; Kelferon; Ferronord; Glyferro; Pleniron. Prepn from glycine and ferrous sulfate: Rummel, U.S. pats. 2,877,253 and 2,957,806 (1959 and 1960 to Dr. Schwarz Arzneimittelfabrik GmbH).

MED USE: In iron deficiency anemia. *Dose:* Oral 1-2 tablets (40-80 mg of ferrous iron). *Side Effects:* G.I. disturbances may occur. *See also* Ferrous Sulfate.

Ferronascin. *2,4-Dihydroxy-3,3-dimethylbutyric acid iron derivative sodium salt*; bis(α, γ -dihydroxy- β, β -dimethylbutyrate)ferric acid sodium salt; sodium bis(α, γ -dihydroxy- β, β -dimethylbutyryl)ferrate. $\text{C}_{12}\text{H}_{20}\text{FeNaO}_8$; mol wt 371.13. C 38.84%, H 5.43%, Fe 15.05%, Na 6.19%, O 34.49%. Prepn: Schneider, U.S. pat. 2,474,989 (1949 to Hoffmann-La Roche).



Brown soln of yellowish-brown solid. The free acid is precipitated from acetone as a pale yellow-brown powder, becoming brown on heating above 150°.

MED USE: Hematinic for iron deficiency anemia. *Dose:* i.v. 2 ml (= 20 mg of iron). *Side Effects:* Thrombosis of the injected vein, headache, flushing, G.I. symptoms may occur.

Consult the cross index before using this section

Database: Medline <1966 to present>

<1>

Unique Identifier

97406844

Authors

Fuks AB. Holan G. Davis JM. Eidelman E.

Title

— Ferric sulfate versus dilute formocresol in pulpotomized primary molars: long-term follow up.

Source

Pediatric Dentistry. 19(5):327-30, 1997 Jul-Aug.

Abstract

H
The aim of this study was to compare the effect of ferric sulfate (FS) to that of dilute formocresol (DFC) as pulp dressing agents in pulpotomized primary molars. Ninety-six primary molars in 72 children were treated by a conventional pulpotomy technique. Fifty-eight teeth were treated by a FS solution for 15 sec, rinsed, and covered by zinc oxide-eugenol paste (ZOE). In another 38 teeth, a cotton pellet moistened with 20% DFC was placed for 5 min, removed, and the pulp stumps were covered by ZOE paste. The teeth of both groups were sealed by a second layer of intermediate restorative material (IRM) and restored with a stainless steel crown. This is a report of the clinical and radiographic examination of 55 teeth dressed with FS and 37 teeth fixed with DFC, that have been treated 6 to 34 months previously (mean 20.5 months). Four teeth were excluded from the study due to failure of the patient to present for recall. Success rates of 92.7% for the FS, and of 83.8% for the DFC were not significantly different. Four teeth (7.2%) of the FS group and two (5.4%) of the DFC group presented internal resorption. Inter-radicular radiolucencies were observed in two teeth of the FS group and three teeth of the DFC group. The latter also presented periapical lesions. Success rates of both groups were similar to those of previous studies utilizing the traditional Buckley's formocresol.

<2>

Unique Identifier

97391944

Authors

Kim S. Rethnam S.

Title

Hemostasis in endodontic microsurgery.

Unique Identifier

93316024

Authors

Jeansonne BG. Boggs WS. Lemon RR.

Title

Ferric sulfate hemostasis: effect on osseous wound healing.
II. With curettage and irrigation.

Source

Journal of Endodontics. 19(4):174-6, 1993 Apr.

Abstract

Hemorrhage control is often a problem for the clinician during osseous surgery. Ferric sulfate is an effective hemostatic agent, but with prolonged application to an osseous defect can cause persistent inflammation and delayed healing. The purpose of this investigation was to evaluate the effectiveness of ferric sulfate as a hemostatic agent and to determine its effect on healing after thorough curettage and irrigation from osseous surgical wounds. Standard size osseous defects were created bilaterally in the mandibles of rabbits. Ferric sulfate was placed in one defect until hemostasis was obtained; the contralateral defect was allowed to fill with blood and clot. After 5 min both defects were curetted and irrigated. The repair of the defects was evaluated histologically at 18 and 46 days. There were no significant differences between the ferric sulfate-treated defects and the untreated controls. When adequately curetted and irrigated from the surgical site prior to closure, ferric sulfate did not cause persistent inflammation or delay osseous repair in comparison to controls.

<6>

Unique Identifier

93316023

Authors

Lemon RR. Steele PJ. Jeansonne BG.

Title

Ferric sulfate hemostasis: effect on osseous wound healing.
Left in situ for maximum exposure.

Source

Journal of Endodontics. 19(4):170-3, 1993 Apr.

Abstract

Ferric sulfate solution is an accepted soft tissue hemostatic agent for use in dermatology and dentistry. This study was designed to test its effect on osseous healing when used during surgery to control osseous hemorrhage. Standardized osseous defects were created bilaterally in the naturally edentulous zone in rabbit mandibles. The

control site was sutured immediately after clot formation in the defect. The contralateral experimental site received ferric sulfate application until complete hemostasis was achieved. The defect was filled with ferric sulfate solution to maximize any effect on healing and then closed with sutures. The experimental and control specimens were examined histologically after 18 and 46 days and scored for healing. Statistical analysis by Wilcoxon signed rank test showed significant adverse effects on osseous healing when ferric sulfate solution was left in situ.

<7>

Unique Identifier

93181319

Authors

Fei AL. Udin RD. Johnson R.

Title

A clinical study of ferric sulfate as a pulpotomy agent in primary teeth.

Source

Pediatric Dentistry. 13(6):327-32, 1991 Nov-Dec.

Abstract

Pulpotomies were performed on 83 primary molars in 62 patients. Ferric sulfate or formocresol was placed on the pulpal stumps, and teeth were followed for 3-, 6-, and 12-month periods. After the one-year follow-up, 28 of 29 teeth treated with ferric sulfate (FS group) were considered successful and 21 of 27 teeth treated with formocresol (FC group) were judged to be successful. The FS group demonstrated greater combined clinical and radiographic success than the FC group at the one-year recall ($P < 0.05$). Although the results of this study are promising, further study with longer observation periods is warranted before this technique can be recommended.

Source

Dental Clinics of North America. 41(3):499-511, 1997 Jul.

Abstract

There are numerous ways to achieve hemostasis. With the abundance of hemostatic agents available and with the introduction of new products, one has to make an objective decision. A good agent achieves hemostasis within a short period of time, is easy to manipulate, is biocompatible, does not impair or retard healing, must be relatively inexpensive, is reliable, and works best for the particular surgical procedure. With these purposes in mind, the following sequence is recommended to achieve hemostasis during endodontic microsurgery. I. Presurgical: Give 2 to 3 Carpules of 1:50,000 epinephrine local anesthetic with multiple infiltration sites throughout the entire surgical field. II. Surgical: A. Remove all granulation tissue. B. Place an epinephrine pellet into the bony crypt followed by dry sterile cotton pellets. Apply pressure for 2 minutes. Remove all the cotton pellets except the first epinephrine pellet. Continue with the surgical procedure and remove the epinephrine pellet before final irrigation and closure. C. Alternatively, calcium sulfate can be mixed into a thick putty and packed against the bone cavity. Because it is a biodegradable material, calcium sulfate can be left in situ. In fact, in large bone defects and through-and-through lesions, additional calcium sulfate can be placed to fill the entire bone cavity as a barrier material. Healing is more predictable with little chance of scar tissue formation. Calcium sulfate resorbs in 2 to 4 weeks. D. Small bleeding sites in the bone can be brushed with ferric sulfate solution. III. Postsurgical: Tissue compression before and after suturing cuts down on postsurgical bleeding and swelling. Hemostasis is imperative in endodontic microsurgery for better visualization, a good environment for placement of retrograde filling material, and a more efficient surgical procedure with less blood loss.

<3>

Unique Identifier

84144452

Authors

Shaw DH. Krejci RF. Kalkwarf KL. Wentz FM.

Title

Gingival response to retraction by ferric sulfate (Astringedent).

Source

Operative Dentistry. 8(4):142-7, 1983 Autumn.

A. INGREDIENT NAME:

GUAIACOL

B. Chemical Name:

Guajacol, Guaiacol, Guaicoo, Guajakol (CZECH), O-Hydroxyanisole, 2-Hydroxyanisole, 1-Hydroxy-2-Methoxybenzene, O-Methoxyphenol, 2-Methoxyphenol, Methylcatechol, Pyroguaiac Acid

C. Common Name:

Austral: Waterbury's Compound, Belg: Baume Dalet, Canada: Cre-Rectal, etc. Various names from different countries. Please see file.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specifications)</i>	<i>(Results)</i>
Assay:	99.5% min.	99.7%

E. Information about how the ingredient is supplied:

White or slightly yellow crystal mass or colorless to yellowish, very refractive liquid, characteristic odor, darkens to exposure to air and light.

F. Information about recognition of the substance in foreign pharmacopeias:

Arg., Braz., Chil., Fr., It., Mex., Port., Roum., Span., and Swiss.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

Expectorant

I. Information about strength:

0.3-0.6ml

J. Information about route of administration:

Orally

K. Stability data:

Boiling Point: 205C

Melting Point: 27C to 29C

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1709

50703

PRODUCT: GUAIACOL LIQUID
RELEASE #: N

LOT # :X49993D28

GRADE: PURIFIED
CODE: R9128201

	<u>SPECIFICATIONS</u> -----	<u>RESULT</u> -----
1. Description	Colorless liquid , characteristic odor	Conforms
2. Solidification point	27.5 deg C min.	28.0 deg C
3. Assay	99.5% min.	99.7% D

ATTENTION: TONY HATCHETT

Date :06/06/97

Prepared by : A.M. Scullion/MS

9257

Approved by :  6/97

Our Order # 234202 Your PO # 52409

QUALITY CONTROL REPORT

CHEMICAL NAME.: GUAIACOL PURIFIED (LIQUID) _____

MANUFACTURE LOT NO.: X49993D28

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

E { WHITE OR SLIGHTLY YELLOW CRYSTAL MASS OR COLORLESS TO YELLOWISH,
VERY REFRACTIVE LIQUID; CHARACTERISTIC ODOR; DARKENS ON EXPOSURE TO
AIR AND LIGHT.

2) SOLUBILITY.:

1gm DISSOLVES IN 60-70ml WATER, 1ml GLYCEROL; MISCIBLE WITH ALCOHOL,
CHLOROFORM, ETHER, OILS, GLACIAL ACETIC ACID; SOLUBLE IN NAOH SOLUTION;
WITH MODERATELY CONC KOH, IT FORMS A SPARINGLY SOLUBLE COMPOUND.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____



Use your web browser's "Back" key to return to previous topic.

MATERIAL SAFETY DATA SHEET

**Guaiacol, 99+%
06742**

****** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ******

MSDS Name: Guaiacol, 99+%

2-Methoxyphenol
Company Identification: Acros Organics N.V.
One Reagent Lane
Fairlawn, NJ 07410

For information in North America, call: 800-ACROS-01
For emergencies in the US, call CHEMTREC: 800-424-9300
For emergencies in the US, call CHEMTREC: 800-424-9300

****** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ******

CAS#	Chemical Name	%	EINECS#
90-05-1	GUAIACOL	99+	201-964-7

Hazard Symbols: XN
Risk Phrases: 22 36/38

****** SECTION 3 - HAZARDS IDENTIFICATION ******

EMERGENCY OVERVIEW

Appearance: clear slightly yellow. Flash Point: 82 deg C.
Light sensitive. Air sensitive.
Target Organs: Central nervous system, eyes, skin.

Potential Health Effects

- Eye:
Causes eye irritation. Causes redness and pain.
- Skin:
Causes severe skin irritation. May be absorbed through the skin.
Causes redness and pain.
- Ingestion:
Harmful if swallowed. May cause gastrointestinal irritation with
nausea, vomiting and diarrhea.
- Inhalation:
May cause respiratory tract irritation.
- Chronic:
Not available.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
 Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid.

Skin:
 Get medical aid. Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:
 Get medical aid. Wash mouth out with water.

Inhalation:
 Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Notes to Physician:
 Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
 As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Combustible Liquid.

Extinguishing Media:
 In case of fire use water spray, dry chemical, carbon dioxide, or chemical foam.

Autoignition Temperature: 385 deg C (725.00 deg F)
 Flash Point: 82 deg C (179.60 deg F)
 NFPA Rating: Not published.
 Explosion Limits, Lower: Not available.
 Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:
 Absorb spill with inert material, (e.g., dry sand or earth), then place into a chemical waste container. Remove all sources of ignition. Use a spark-proof tool.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
 Avoid breathing dust, vapor, mist, or gas. Avoid contact with skin and eyes. Use only in a chemical fume hood.

Storage:
 Keep away from sources of ignition. Store in a cool, dry place. Do not store in direct sunlight. Store in a tightly closed container.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:
 Use adequate ventilation to keep airborne concentrations low.

Exposure Limits			
Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
GUAIACOL	none listed	none listed	none listed

OSHA Vacated PELs:
 GUAIACOL:
 No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:
 Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:
Wear appropriate protective gloves to prevent skin exposure.

Clothing:
Wear appropriate protective clothing to prevent skin exposure.

Respirators:
Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State: Liquid
Appearance: clear slightly yellow
Odor: Aromatic odor
pH: Not available.
Vapor Pressure: 7 hPa @ 79 deg C
Vapor Density: 4.3
Evaporation Rate: Not available.
Viscosity: Not available.
Boiling Point: 205 deg C @ 760.00mm Hg
Freezing/Melting Point: 27 - 29 deg C
Decomposition Temperature: Not available.
Solubility: 1.7 G/100ML WATER (15°C)
Specific Gravity/Density: 1.1290g/cm3
Molecular Formula: C7H8O2
Molecular Weight: 124.14

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:
Stable under normal temperatures and pressures.

Conditions to Avoid:
Incompatible materials, light, exposure to air.

Incompatibilities with Other Materials:
Strong oxidizing agents - strong bases - acid chlorides - acid anhydrides.

Hazardous Decomposition Products:
Carbon monoxide, carbon dioxide.

Hazardous Polymerization: Will not occur.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
CAS# 90-05-1: SL7525000

LD50/LC50:
CAS# 90-05-1: Inhalation, mouse: LC50 =7570 mg/m3; Oral, mouse: LD50 = 621 mg/kg; Oral, rat: LD50 = 520 mg/kg; Skin, rabbit: LD50 = 4600 mg/kg.

Carcinogenicity:
GUAIACOL -
Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
EC 50 (24 hr) Daphnia magna: 63 mg/l

Environmental Fate:
Guaiacol is biodegradable.

Physical/Chemical:
Not available.

Other:
Not available.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: Not listed.

RCRA U-Series: Not listed.

Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT

No information available

IMO

Not regulated as a hazardous material.

IATA

Not regulated as a hazardous material.

RID/ADR

Not regulated as a hazardous material.

Canadian TDG

No information available.

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA

CAS# 90-05-1 is listed on the TSCA inventory.

Health & Safety Reporting List

None of the chemicals are on the Health & Safety Reporting List.

Chemical Test Rules

None of the chemicals in this product are under a Chemical Test Rule.

Section 12b

None of the chemicals are listed under TSCA Section 12b.

TSCA Significant New Use Rule

None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)

None of the chemicals in this material have an RQ.

Section 302 (TPQ)

None of the chemicals in this product have a TPQ.

SARA Codes

CAS # 90-05-1: acute, flammable.

Section 313

No chemicals are reportable under Section 313.

Clean Air Act:

This material does not contain any hazardous air pollutants.

This material does not contain any Class 1 Ozone depletors.

This material does not contain any Class 2 Ozone depletors.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.

None of the chemicals in this product are listed as Priority

Pollutants under the CWA.

None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

Not present on state lists from CA, PA, MN, MA, FL, or NJ.

California No Significant Risk Level:

None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: XN

Risk Phrases:

R 22 Harmful if swallowed.

R 36/38 Irritating to eyes and skin.

Safety Phrases:

S 26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

WGK (Water Danger/Protection)

CAS# 90-05-1: 1

Canada

CAS# 90-05-1 is listed on Canada's DSL/NDSL List.

WHMIS: Not available.

CAS# 90-05-1 is listed on Canada's Ingredient Disclosure List.

Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 11/03/1991 Revision #2 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

[Back to product information.](#)

BY-1788

A colourless, corrosive liquid with a pungent odour; weight per ml, about 1.22 g.

Formic Acid Solution, Non-aqueous A 5% w/v solution of *anhydrous formic acid* in *chloroform*.

Non-aqueous Formic Acid Solution should be freshly prepared; it is an extremely corrosive material.

D-Fructose Laevulose; $C_6H_{12}O_6 = 180.2$

General reagent grade of commerce.

A white, crystalline powder; melting point, about 103° with decomposition; $[\alpha]_D^{20}$, about -92° (10% w/v in water containing 0.05 ml of 5M ammonia).

L-Fucose 6-Deoxy-L-galactose; $C_6H_{12}O_5 = 164.2$

General reagent grade of commerce.

A white powder; melting point, about 140° ; $[\alpha]_D^{20}$, about -76° (9% w/v in water measured after 24 hours).

Furfuraldehyde Furfural; furan-2-aldehyde;

$C_5H_4O_2 = 96.09$

General reagent grade of commerce.

A colourless or pale brownish-yellow, oily liquid; boiling point, about 162° ; weight per ml, about 1.16 g.

D-Galactose $C_6H_{12}O_6 = 180.2$

General reagent grade of commerce.

A white, crystalline powder; melting point, about 164° ; $[\alpha]_D^{20}$, about $+80^\circ$ (10% w/v in water).

Gallic Acid 3,4,5-Trihydroxybenzoic acid; $C_7H_6O_5, H_2O = 188.1$

General reagent grade of commerce.

Melting point, about 260° .

Gelatin Of the British Pharmacopœia.

Gelatin, Pancreatic Digest of

Microbiological reagent grade of commerce.

Gitoxin $C_{41}H_{64}O_{14} = 781.0$

General reagent grade of commerce.

A white, crystalline powder; melting point, about 283° , with decomposition; $[\alpha]_D^{20}$, about $+22^\circ$ (0.5% w/v in a mixture of equal volumes of chloroform and methanol).

Complies with the following test.

HOMOGENEITY Carry out test A for Identification described under *Digitalis Leaf* applying to the chromatoplate a solution containing only the reagent being examined. The chromatogram shows only one spot.

D-Glucose Dextrose; $C_6H_{12}O_6 = 180.2$

Analytical reagent grade of commerce.

A white, crystalline or granular powder; $[\alpha]_D^{20}$, about $+52.5^\circ$ (10% w/v in water containing 0.2 ml of 5M ammonia).

D-Glucose Monohydrate $C_6H_{12}O_6, H_2O = 198.2$

General reagent grade of commerce.

Colourless crystals or a white to cream, crystalline powder; $[\alpha]_D^{20}$, about $+52.5^\circ$ (10% w/v in water containing 0.2 ml of 5M ammonia).

Glycerol Propane-1,2,3-triol; $HOCH_2 \cdot CHOH \cdot CH_2OH = 92.10$

Analytical reagent grade of commerce.

A colourless viscous liquid; weight per ml, about 1.26 g.

Glycerol (85%) Glycerol containing 12.0 to 16.0% w/w of water; weight per ml, 1.22 to 1.24 g.

Glycerol Triacetate Triacetin; $C_9H_{14}O_6 = 218.2$

General reagent grade of commerce.

A colourless liquid; weight per ml, about 1.16 g.

Glycine Aminoacetic acid; $H_2NCH_2 \cdot CO_2H = 75.1$

Analytical reagent grade of commerce.

Glycollic Acid Hydroxyacetic acid; $HOCH_2 \cdot CO_2H = 76.05$

General reagent grade of commerce.

Slightly hygroscopic crystals; melting point, about 80° .

Glycyrrhetic Acid Glycyrrhetic acid; a mixture of α - and β -isomers with the β -isomer predominating; $C_{30}H_{46}O_4 = 470.7$

General reagent grade of commerce.

A white to brownish-yellow powder; melting point, about 292° , with decomposition; $[\alpha]_D^{20}$, about $+160^\circ$ (1% w/v in chloroform).

β -Glycyrrhetic Acid 3β -Hydroxy-11-oxo-18 β ,20 β -olean-12-enoic acid; $C_{30}H_{46}O_4 = 470.7$

General reagent grade of commerce.

Melting point, about 293° ; $[\alpha]_D^{20}$, about $+170^\circ$ (1% w/v in chloroform).

Glyoxal Bis(2-hydroxyanil) Bis(2-hydroxyphenylimino)-ethane; $C_{14}H_{12}N_2O_2 = 240.3$

General reagent grade of commerce.

Melting point, about 200° .

Glyoxal Sodium Bisulphite

$(HOCH \cdot SO_2Na)_2, H_2O = 284.2$

General reagent grade of commerce.

A white or cream powder.

Gonadotrophin, Chorionic

General reagent grade of commerce.

A white or almost white, amorphous powder.

Gonadotrophin, Serum

General reagent grade of commerce.

A white or pale grey, amorphous powder.

Green S CI 44090; E142; lissamine green; acid brilliant green BS

Indicator grade of commerce.

Guaiacol *o*-Methoxyphenol; $CH_3O \cdot C_6H_4 \cdot OH = 124.1$

General reagent grade of commerce.

Colourless or pale yellow or pink crystals with an aromatic odour; melting point, about 28° .

Guaiacol Solution A 5% w/v solution of *guaiacol* in *ethanol* (96%).

Guaiacol Solution should be protected from light.

Guaiacum Resin Resin obtained from the heartwood of *Guaiacum officinale* L. and *Guaiacum sanctum* L.

Reddish-brown or greenish-brown, glassy fragments.

Guaiacum Tincture Macerate in a stoppered flask 20 g of *guaiacum resin* with 100 g of *ethanol* (80%) for 24 hours, shaking occasionally, and filter.

Guaiazulene 1,4-Dimethyl-7-isopropylazulene; $C_{15}H_{18} = 198.3$

General reagent grade of commerce.

Dark blue crystals or a blue liquid; melting point, about 29° .

Guaiazulene should be protected from light and air.

Guanine 2-Aminopurin-6-one; $C_5H_4N_4O = 151.1$

General reagent grade of commerce.

Heavy Metals Masking Solution To 2.0 ml of 2M ammonia add, in the following order, 1.5 ml of a 5% w/v solution of *ammonium oxalate*, 15 ml of a 5% w/v solution of *potassium cyanide*, 45 ml of a 10% w/v solution of *sodium acetate*, 120 ml of a 50% w/v solution of *sodium thiosulphate*, 75 ml of a 10% w/v solution of *sodium acetate* and 35 ml of 1M *hydrochloric acid*.

Heavy Metals Masking Solution should be prepared immediately before use.

PREPARATIONS

Euphorbia Liquid Extract (B.P.C. 1949). Ext. Euphorb. Liq. 1 in 1; prepared by percolation with alcohol (45%). *Dose*: 0.12 to 0.3 ml.

Mist. Euphorb. Co. (N.F. 1939). Euphorbia liquid extract 0.6 ml, potassium iodide 450 mg, sodium bromide 450 mg, glyceryl trinitrate solution 0.06 ml, ethereal lobelia tincture 0.4 ml, water to 15 ml. *Dose*: 15 ml.

AMENDED FORMULA. Euphorbia liquid extract 0.5 ml, potassium iodide 450 mg, sodium bromide 450 mg, glyceryl trinitrate solution 0.05 ml, ethereal lobelia tincture 0.4 ml, water to 10 ml.—*Compendium of Past Formulae 1933 to 1966*. London. The National Pharmaceutical Union, 1969.

NOTE. **Euphorbium** (B.P.C. 1934, *Neth.P.*, *Nord.P.*, *Port.P.*, *Span.P.*, *Swiss P.*) is the dried latex from the stem of *Euphorbia resinifera*. It is emetic and powerfully purgative but it is not used internally on account of its violent action and its tendency to cause acute nephritis. The powder is violently sternutatory. Externally, it acts as a vesicant and was used for this purpose in veterinary medicine.

Garlic (B.P.C. 1949, *Span. P.*). *Allium*; Ail.

The fresh bulb of *Allium sativum* (Liliaceae). It has a very strong and disagreeable odour and a strongly pungent and persistent taste. It yields 0.1 to 0.3% of a volatile oil containing allyl propyl disulphide and diallyl disulphide. **Stored** in a cool dry place with free access of air it may be kept for about 6 months after harvesting.

Garlic has expectorant, diaphoretic, disinfectant, and diuretic properties, and the juice was formerly used alone or in a syrup in the treatment of pulmonary conditions. **Precautions**: administration of preparations of garlic to children is dangerous and fatalities have been recorded. *Dose*: 2 to 8 g.

The larvicidal principles of garlic active against the *Culex* mosquito were found to be diallyl di- and trisulphides. Natural and synthetic samples proved fatal at 5 ppm.—S. V. Amonkar and A. Banerji, *Science, Wash.*, 1971, 174, 1343.

A report of allergic contact dermatitis to garlic.—E. Bleumink *et al.*, *Br. J. Derm.*, 1972, 87, 6.

Garlic juice and the extracted essential oil prevented the hyperlipaemia and blood coagulation changes following fat ingestion in 5 healthy subjects.—A. Bordia and H. C. Bansal (letter), *Lancet*, ii/1973, 1491.

HYPERTENSION. In 5 consecutive cases of hypertension, garlic reduced the blood pressure to satisfactory levels.—V. Srinivasan (letter), *Lancet*, ii/1969, 800.

PREPARATIONS

Garlic Juice (B.P.C. 1949). Succus Allii. Bruise garlic 80 g and express the juice; mix the marc with water 20 ml and again express the liquid; repeat the operation until the volume of the mixed juice and washings amounts to 80 ml, and add alcohol (90%) 20 ml; allow to stand for 14 days, and decant or filter. *Dose*: 2 to 4 ml.

Garlic Syrup (B.P.C. 1949). Syr. Allii. Garlic juice 20 ml, sucrose 80 g, dilute acetic acid 20 ml, water 20 ml. *Dose*: 2 to 8 ml.

Grindelia (B.P.C. 1949). *Grindelia Robusta*; Gum Plant; Gumweed; Tar Weed.

Foreign Pharmacopoeias: In *Span.* In *Belg.* and *Braz.* which allow also the dried leaves and flowering tops of the marsh gumweed, *G. humilis*, and of the curly-cup gumweed, *G. squarrosa*. In *Fr.* and *Port.* which allow also *G. squarrosa*.

The dried leaves and flowering tops of the field gumweed, *Grindelia camporum* (Compositae) containing not less than 20% of alcohol (90%)-soluble extractive. **Store** in a cool dry place.

Grindelia has expectorant properties and has been stated to exert a spasmolytic effect. It has been used as a liquid extract in the treatment of asthma and bronchitis. Large doses sometimes cause renal irritation. Its nauseous taste may be masked with chloroform or glycerol.

PREPARATIONS

Grindelia Liquid Extract (B.P.C. 1949). Ext. Grindel. Liq. *Grindelia* 100 g is exhausted by percolation with alcohol (90%), the alcohol is removed by distillation, and the residue is dissolved in water 50 ml to which 10 g of sodium bicarbonate has previously been added; after effervescence has ceased, the solution is adjusted to 100 ml with alcohol (90%) and filtered. *Dose*: 0.6 to 1.2 ml.

Guaiaicol (B.P.C. 1949). Gaiaicol; Methyl Catechol.

Foreign Pharmacopoeias: In *Arg.*, *Braz.*, *Chil.*, *Fr.*, *It.*, *Mex.*, *Port.*, *Roum.*, *Span.*, and *Swiss*.

A colourless or almost colourless oily liquid or crystals with a penetrating aromatic odour and a caustic taste, obtained as a liquid by fractional distillation of wood-tar creosote or, usually as crystals, by synthesis.

The main constituent is *o*-methoxyphenol, $\text{CH}_3\text{O.C}_6\text{H}_4.\text{OH} = 124$. Wt per ml (liquid) about 1.12 g; m.p. (crystals) about 28°. It tends to become yellowish on exposure to light.

Soluble 1 in 80 of water; miscible with alcohol, chloroform, ether, glacial acetic acid, and fixed and volatile oils; soluble 1 in 1 of glycerol but separates out on the addition of water. **Incompatible** with ferric salts. **Protect** from light.

Guaiaicol has disinfectant properties similar to those of creosote. It has been used as an expectorant. **Toxic effects**: as for Phenol, p. 529. *Dose*: 0.3 to 0.6 ml.

Guaiaicol Carbonate (B.P.C. 1949). Duotal. $(\text{CH}_3\text{O.C}_6\text{H}_4.\text{O})_2.\text{CO} = 274.3$.

Foreign Pharmacopoeias: In *Chil.*, *Port.*, and *Span.*

Guaiaicol carbonate is the carbonic ester of guaiaicol. It is a white, almost odourless, tasteless, crystalline powder. M.p. 83° to 88°.

Insoluble in water; soluble 1 in 70 of alcohol and 1 in 20 of ether; readily soluble in chloroform; slightly soluble in glycerol and fixed oils. It is decomposed by alcoholic potassium hydroxide solution and guaiaicol separates from the solution on the addition of excess acid.

Guaiaicol carbonate has the actions of guaiaicol but is less irritant. It liberates guaiaicol slowly and incompletely in the intestines, the larger part passing through the alimentary tract unchanged. *Dose*: 0.3 to 1 g.

Guaiphenesin (B.P.C.). Guaiaicyl Glyceryl Ether; Guaiaicol Glycerol Ether; Guaifenesin (U.S.N.F.); Glyceryl Guaiaicolate; Glycerylguaiacolum. 3-(*o*-Methoxyphenoxy)propane-1,2-diol. $\text{C}_{10}\text{H}_{14}\text{O}_4 = 198.2$.

Foreign Pharmacopoeias: In *Cz.* and *Roum.* Also in *U.S.N.F.*

Dose: 100 to 200 mg every 2 to 4 hours.

White odourless or almost odourless crystals or crystalline aggregates with a bitter taste. M.p. 80° to 82°.

Soluble 1 in 33 of water at 20°, 1 in 11 of alcohol and 1 in 3 of chloroform, and 1 in 200 of ether; soluble 1 in 15 of glycerol with warming, 1 in 15 of propylene glycol, and 1 in 80 of sorbitol syrup. A 2% solution in water has a pH of 5 to 7, and is clear and colourless. Aqueous solutions are stable and may be sterilised by autoclaving. **Store** in airtight containers.

Toxic Effects and Precautions. Side-effects are rare with guaiphenesin. Gastro-intestinal discomfort and drowsiness have been reported.

A metabolite of guaiphenesin was found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaiphenesin could thus interfere with the diagnosis of the carcinoid syndrome. Asthma patients being evaluated for the carcinoid syndrome should therefore discontinue any preparation containing guaiphenesin for 24 hours before the collection of urine specimens for the determination of 5-hydroxyindoleacetic acid. Acetanilide, mephenesin, and methocarbamol had been reported to cause similar false positive reactions, and hexamine methanolate and some phenothiazine derivatives to cause false negative reactions.—A. T. Pedersen *et al.*, *J. Am. med. Ass.*, 1970, 211, 118. See also P. D. Reeme, *Hosp. Formul. Mgmt.*, 1970, 5, 15, per *Int. pharm. Abstr.*, 1973, 10, 26.

Hypouricaemia (serum-urate concentrations of less than 20 µg per ml) in 6 patients could have been due to guaiphenesin. Therapeutic doses for 3 days reduced serum urate by up to 30 µg per ml in 4 patients.—C. Ramsdell and W. N. Kelley, *Ann. intern. Med.*, 1973, 78, 239.

Absorption and Fate. Guaiphenesin is readily absorbed from the gastro-intestinal tract. It is rapidly metabolised and excreted in the urine.

Guaiphenesin was rapidly absorbed from the gastro-intestinal tract; blood concentrations of 1.4 µg per ml occurring 15 minutes after a dose of 600 mg in 3 healthy fasting men. It was rapidly eliminated from the circulation, having a half-life of 1 hour, and was not detectable in blood after 8 hours.—W. R. Maynard and R. B. Bruce, *J. pharm. Sci.*, 1970, 59, 1346.

The major urinary metabolite of guaiphenesin was identified as *o*-methoxyphenoxy)lactic acid.—W. J. A. VandenHeuvel *et al.*, *J. pharm. Sci.*, 1972, 61, 1997.

Uses. Guaiphenesin is reported to reduce the viscosity of tenacious sputum and is used as an expectorant in cough linctus and tablets.

When given by mouth or by injection in large doses, guaiphenesin has a relaxant effect on skeletal muscle similar to that of mephenesin which it closely resembles structurally. This effect is not produced by the doses normally employed in the treatment of cough.

tics

teine (2948-y)

(HNN)
rahe...oxo-3-thienyl]carbamoyl]methyl]thio-
...
C₁₄H₁₂N₂O₄S₂ = 449.3.
4611-23-4.

ne is being studied for use as a mucolytic

lictyon (2012-e)

Balm; Yerba Santa.
8013-08-9.

nd leaves of *Eriodictyon californicum* (Hydrophyl-

ctyon has been used as an expectorant. It has
en used to mask the taste of bitter drugs.

irations

of preparations are listed below; details are given in Part 3.

itary Preparations

redient preparations. Ger.: Mistelant; Ital.: Bronco-

yl Cysteine Hydrochloride

k)
-2-amino-3-mercaptopropionate hydrochloride.
NO₂S.HCl = 185.7.
— 3411-58-3 (ethyl cysteine); 868-59-7 (ethyl
ne hydrochloride).

l cysteine hydrochloride is a mucolytic agent
p.1059) used in the treatment of disorders of the
rahe...ct associated with excessive or vis-
mu... A daily dose of 600 to 900 mg has been
n by mouth in 2 or 3 divided doses.

parations

es of preparations are listed below; details are given in Part 3.

rietary Preparations

udixant*.

hyl Orthoformate (5618-t)

de Kay; Triethoxymethane. Triethyl orthoformate.
C₆H₁₄O₃ = 148.2.
— 122-51-0.
macropoeias. In Fr.

yl orthoformate is a cough suppressant (see
059). It is reported to be a respiratory antispas-
dic and is administered by mouth or rectally.

eparations

es of preparations are listed below; details are given in Part 3.

roprietary Preparations

g.: Aethone; Fr.: Aethone.

ulti-ingredient preparations. Switz.: Rectoquintyl; Recto-

intyl-Promethazine.

edrilate (5619-x)

edrilate (HNN).
edrilatum; UCB-3928. 1-Methyl-3-morpholinopropyl perhy-
ro-4-phenylpyran-4-carboxylate.
C₂₀H₂₉NO₄ = 347.5.
AS — 23271-74-1.

ed...s a cough suppressant (see p.1059) which
as... given by mouth as the maleate in doses of
50 mg three to six times daily.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

S.Afr.: Corbar S; Dykaruss "S"†.

Multi-ingredient preparations. Ger.: Duotal†.

Fominoben Hydrochloride (5620-z)

Fominoben Hydrochloride (HNNM).
PB-89. 3'-Chloro-2'-[N-methyl-N-(morpholinocarbonyl-
yl)aminomethyl]benzanilide hydrochloride.
C₂₁H₂₄ClN₃O₃.HCl = 438.4.
CAS — 18053-31-1 (fominoben); 24600-36-0 (fominoben
hydrochloride).

Fominoben hydrochloride is a centrally acting
cough suppressant (see p.1059) which is also report-
ed to have respiratory stimulant properties. It is giv-
en in doses of 160 mg two or three times daily by
mouth; it has also been given by slow intravenous
injection.

References.

- 1. Sasaki T, et al. Effects of the antitussive fominoben (PB89) on
hypoxia in chronic obstructive lung disease: comparison
with dextromethorphan using a double-blind method. *J Int Med* 1985;
13: 96-101.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Ger.: Noleptant; Ital.: Tenont; Spain: Broncomenalt; Taiwan:
Tosifar.

Multi-ingredient preparations. Ger.: Broncho-Noleptan

Glaucine (19251-g)

Boldine Dimethyl Ether; DL-832 (dl-glaucine phosphate);
Glaucine; MDL-832 (dl-glaucine phosphate). DL-1,2,9,10-
tramethoxyaporphine.
C₂₁H₂₅NO₄ = 355.4.
CAS — 5630-11-5 (dl-glaucine); 73239-87-9 (dl-glaucine
phosphate); 475-81-0 (d-glaucine); 5996-06-5 (d-glaucine
hydrobromide).

Glaucine is a centrally acting cough suppressant
(see p.1059) which has been studied as the phos-
phate.

d-Glaucine has been used as the hydrobromide
the hydrochloride as a cough suppressant in eastern
Europe. It has been obtained from *Glaucium flavum*
(Papaveraceae).

References.

- 1. Redpath JBS, Pleuvry BJ. Double-blind comparison of the
respiratory and sedative effects of codeine phosphate and
glaucine phosphate in human volunteers. *Br J Clin Pharmacol* 1982;
14: 555-8.
- 2. Rühle KH, et al. Objective evaluation of dextromethorphan
and glaucine as antitussive agents. *Br J Clin Pharmacol* 1984; 17:
521-4.
- 3. Gasipar H, et al. Efficacy and tolerability of glaucine as
an antitussive agent. *Curr Med Res Opin* 1984; 9: 21-7.

Guacetisal (12801-w)

Guacetisal (HNN).
Acetylsalicylic Acid Guaiacol Ester. o-Methoxyphenyl salicylic
acetate.
C₁₆H₁₄O₅ = 286.3.
CAS — 55482-89-8.

Guacetisal has been used in respiratory disorders
as an expectorant (see p.1059). It has also been used
as an antipyretic to reduce fever, the more usual treat-
ment of which is discussed on p.2. Doses of 500 mg
have been administered by mouth two to three times
daily. It has also been administered rectally.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Ital.: Balsacetil; Broncaspin; Guaiaspir; Guajabronc; Pronomax

Guajacol (2016-z)

Guajacol; Methyl Catechol.
CAS — 90-05-1 (guaiacol); 553-17-3 (guaiacol carbon-
ate); 60296-02-8 (calcium guaiacolglycolate); 4112-89-
(guaiacol phenylacetate).
Pharmacopoeias. In Belg., Fr., and Swiss. Fr. also includes Guai-
acol Carbonate.

The main constituent of guajacol is 2-methoxyphenol.
C₇H₆O₂.OH = 124.1.

Guaiacol has disinfectant properties and has been
used as an expectorant (see p.1059).

Adverse effects are similar to those of Phenol,
p.1141.

A wide range of salts and derivatives of guaiacol
have been used similarly including the carbonate,
cinnamate, ethylglycolate, calcium and sodium gly-
colates, phenylacetate, and phenylbutyrate. See also
Guaiphenesin, p.1069 and Potassium Guaiacolsul-
fonate, p.1074.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Ger.: Anasilt†.

Multi-ingredient preparations. Austral.: Waterbury's Com-
pound; Belg.: Baume Dalet; Eboxolt; Eucalyptine Le Brun; Eucal-
yptine Pholcodine Le Brun; Inalptin; Canad.: Creso-Rectal; Demo-
Cincolt; Dolocent; Omni-Tuss; Valda; Etre; Valda; Fr.: Baume
Dalel; Biocalyptol; Bi-Qui-Nol; Bronchodermine; Bronchorectine
Dalel; Biocalyptol Quinine†; Camphocalyptol Simple†;
Campho-Pneumine; Elixir Dupeyroux†; Essence Algérienne; Eucal-
yptine Aspireine Quinine†; Eucalyptine Le Brun; Eucalyptine
Pholcodine; Eucalyptospirine†; Gaiarsol; Pulmosarin†; Rec-
tophérol; Sirop Boie; Tieucauly†; Valda; Ger.: Anasilt Camphert;
Anasilt; Cobed†; Dalel-Balsam; Perix†; Transpulmin; Zynedo-
Br; Zynedo-K†; Ital.: Auricovert; Biopulmint; Bronco Valda†;
Eucalyptina; Fostoguaicol; Glicocinnaminat; Guaiadomust†;
Katsama Balsamico†; Lactocol; Lipobalsamo; Oiocanam†; Otor-
mon F (Feminile)†; S.Afr.: Cocilix†; Spain: Anginum†; Anuler-
in Balsamico†; Bimoxi Mucolítico; Bronco Aseptilex; Bronco
Aseptilex Fuerte; Bronco Aseptilex Tetra†; Broncolitic†; Bronqui-
mar; Bronquimar NF†; Bronquimar Vit A; Edusan Fe Rectal; Eucal-
yptospirine; Eucalyptospirine Lact; Maboterpen; Pulmo Grey
Balsam; Pulmo Hidratol†; Tos. Mar; Switz.: Bronchodermine;
Bronchorectine; Carmol "blanche"†; Libérol; Rectoseptal-Néo
Pholcodine; Rectoseptal-Néo simple; UK: Dragon Balm; Pulmo
Bally; Valda; USA: Methagual.

Guaiapate (12803-l)

Guaiapate (USAN, HNN).
MG-5454. 1-[2-[(2-(2-Methoxyphenoxyethoxy)ethoxy]je-
thyl]piperidine.
C₁₈H₂₉NO₄ = 323.4.
CAS — 852-42-6.

Guaiapate has been used as a cough suppressant. It
is reported to have central actions.

Gualetolin (12795-v)

Gualetolin (HNN).
Glycerylguethol; Glyguetol. 3-(2-Ethoxyphenoxy)propane-
1,2-diol.
C₁₁H₁₆O₄ = 212.2.
CAS — 63834-83-3.

Gualetolin is an analogue of guaiphenesin which is
used as an expectorant (see p.1059). It has been giv-
en by mouth in doses of 300 to 600 mg two to three
times daily.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Guethural.

Guaimosal (1749-r)

Guaimosal (HNN).
(±)-2-(6-Methoxyphenoxy)-2-methyl-1,3-benzodioxan-4-
one.
C₁₆H₁₄O₅ = 286.3.
CAS — 81674-79-5.

Guaimosal is reported to have anti-inflammatory,
antipyretic, analgesic, and mucolytic properties and
has been given by mouth in a usual dose of 500 mg
two to three times daily as an adjunct in the treat-
ment of acute and chronic infections of the respira-
tory tract. It has also been administered rectally in
suppositories.

Guaimosal has been reported to improve fever, cough fre-
quency and intensity, and sputum viscosity in patients with
acute or chronic bronchitis.¹ However, as stated in the discus-
sion on the management of cough (see p.1059) mucolytics are

generally considered to
more effective nonan-
p.1567.

1. Jager EGH. Double-b-
tion of guaimosal in o-

Preparations

Names of preparations are listed below; details are given in Part 3.
Proprietary Preparations. Ital.: Bronteri.

Guaiphenesin

Guaiphenesin (BAN).
Glyceryl Guaiacolate;
Ether; Guaiaquil Glyce-
Guaifenesina; Guaifene-
3-(2-Methoxyphenoxy-
C₁₀H₁₄O₄ = 198.2.
CAS — 93-14-1.

Pharmacopoeias. In Au-
Port., Swiss, and US.

The standards of Ph. E-
ties to the Convention
macropoeia, see p.xiii.

A white or slightly gr-
a slight characteristic
BP solubilities are: s-
cohol and in chlorofo-
bilities are: soluble 1
in chloroform, and in
glycerol. A 1% soluti-
syrup has a pH of 2.5

Adverse Effect

Gastro-intestinal
reported with gua-
nausea and vomit:

Pharmacokinetics

Guaiphenesin is a
tract. It is metabo-

Uses and Adm-

Guaiphenesin is ;
tenacious sputum
(p.1059). It has be-
to 400 mg every -
dren aged 2 to 6
It has been used -

Infertility. Guaiph-

tility in women with
cervical mucus.¹ TI
mention of this use

1. Check JH, et al. In
esin. *Fertil Steril* ;

Respiratory disor-

tions available
in was an effective
discussed on p.105

1. Thomas J. Guaiph-
tive. *Aust J Pharm*

Uricosuric action

rum-urate concentr-
effect in these patie-
ered to be clinically:

1. Ramsdell CM, et al.
J Rheumatol 1974

2. Matheson CE, et al.
tion on serum uric

Preparations

Names of preparati-
Official Preparati-
USP 23: Dyphyllin

Guaifenesin Tablets
Guaifenesin and P
Guaifenesin Capsul-

ride, and Dextrome-
in Syrup; Guaifene-
Capsules; Theophy-

Proprietary Prep-
Aust.: Guafen; Myr-
er; Austral.: Robit-
Expectorant; Canad-
Expectorant; Resyl-
posyrup expector-
Nephuton G; Robit-
Robitussin; S.Afr.:

The symbol † denotes a preparation no longer actively marketed

times, the larger part passing through the alimentary tract unchanged.

2018-k

Guaiphenesin (B.P.). Guaiacyl Glyceryl Ether; Guaiacol Glycerol Ether; Guaifenesin (U.S.P.); Glyceryl Guaiacolate; Glycerylguayacolium; Guaiacolum Glycerolatum. 3-(2-Methoxyphenoxy)propane-1,2-diol. $C_{10}H_{14}O_4 = 198.2$.

CAS — 93-14-1.

Pharmacopoeias. In Aust., Br., Cz., Roum., and U.S.

White or slightly grey crystals or crystalline aggregates, odourless or with a slight characteristic odour and with a bitter taste. M.p. 78° to 82° with a range of not more than 3° .

Soluble 1 in 33 of water at 20° , 1 in 11 of alcohol and of chloroform, and 1 in 100 of ether; soluble 1 in 15 of glycerol with warming, 1 in 15 of propylene glycol, and 1 in 80 of sorbitol syrup. A 2% solution in water has a pH of 5 to 7. Aqueous solutions are stable and may be sterilised by autoclaving. Store in airtight containers.

Adverse Effects and Precautions. Gastro-intestinal discomfort and drowsiness have been reported. Very large doses cause nausea and vomiting.

A metabolite of guaiphenesin was found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaiphenesin could thus interfere with the diagnosis of the carcinoid syndrome. Patients being evaluated for the carcinoid syndrome should therefore discontinue any preparation containing guaiphenesin for 24 hours before the collection of urine specimens for the determination of 5-hydroxy indoleacetic acid. Acetanilide, mephenesin, and methocarbamol had been reported to cause similar false positive reactions, and hexamine mandelate and some phenothiazine derivatives to cause false negative reactions.— A. T. Pedersen *et al.*, *J. Am. med. Ass.*, 1970, 211, 1184. See also P. D. Reeme, *Hosp. Formul. Mgmt.*, 1970, 5, 15, per *Int. pharm. Abstr.*, 1973, 10, 26.

Hypouricaemia (serum-urate concentrations of less than $20 \mu\text{g}$ per ml) in 6 patients could have been due to guaiphenesin. Therapeutic doses for 3 days reduced serum urate by up to $30 \mu\text{g}$ per ml in 4 patients.— C. M. Ramsdell and W. N. Kelley, *Ann. intern. Med.*, 1973, 78, 239.

Absorption and Fate. Guaiphenesin is readily absorbed from the gastro-intestinal tract. It is rapidly metabolised and excreted in the urine.

Guaiphenesin was rapidly absorbed from the gastro-intestinal tract, blood concentrations of $1.4 \mu\text{g}$ per ml occurring 15 minutes after a dose of 600 mg in 3 healthy fasting men. It was rapidly eliminated from the circulation, having a half-life of 1 hour, and was not detectable in the blood after 8 hours.— W. R. Maynard and R. B. Bruce, *J. pharm. Sci.*, 1970, 59, 1346.

The major urinary metabolite of guaiphenesin was identified as β -(2-methoxyphenoxy)lactic acid.— W. J. A. VandenHeuvel *et al.*, *J. pharm. Sci.*, 1972, 61, 1997.

Uses. Guaiphenesin is reported to reduce the viscosity of tenacious sputum and is used as an expectorant. It has been given in doses of 100 to 200 mg every 2 to 4 hours.

When given by mouth or by injection in large doses, guaiphenesin has a relaxant effect on skeletal muscle similar to that of mephenesin which it closely resembles structurally, but this effect is not produced by the doses normally employed in the treatment of cough.

Guaiphenesin was no better than water in lowering the viscosity of 27 sputum specimens obtained from chronic bronchitics. Doses of 0.8 to 1.6 g daily had no effect on sputum or respiratory function when compared with placebo in 11 patients with chronic bronchitis.— S. R. Hirsch *et al.*, *Chest*, 1973, 63, 9.

From a study in 239 patients it was reported that guaiphenesin reduced cough frequency and intensity in patients with dry or productive cough, and helped to thin sputum, when compared to placebo.— R. E. Robinson *et al.*, *Robins, Curr. ther. Res.*, 1977, 22, 284.

A report of a double-blind crossover study in 19 patients with chronic bronchitis showed that guaiphenesin was

not significantly better than a placebo in aiding clearance of secretion from the lungs.— D. B. Yeates *et al.*, *Am. Rev. resp. Dis.*, 1977, 115, Suppl. 4, 182.

Effects on blood. A dose of 200 mg of guaiphenesin was found to prolong the activated-plasma clotting time in 22 healthy volunteers. The same dose, given to 12 healthy volunteers, was found to reduce platelet adhesiveness significantly.— R. D. Eastham and E. P. Griffiths, *Lancet*, 1966, 1, 795.

Guaiphenesin 200 mg given as a single dose to 5 healthy subjects was associated with transient abnormality in platelet aggregation patterns determined 1 hour after ingestion, showing some inhibition of secondary aggregation but less marked than that observed in other subjects given chlorpromazine or aspirin. Mean bleeding times as determined by a modified Ivy technique were prolonged by single doses of aspirin but were not affected by guaiphenesin; thrice-daily doses of indomethacin given for 3 days caused some prolongation.— G. R. Buchanan *et al.*, *Am. J. clin. Path.*, 1977, 68, 355.

Preparations

Guaifenesin Capsules (U.S.P.). Capsules containing guaiphenesin. Store in airtight containers.

Guaifenesin Syrup (U.S.P.). A syrup containing guaiphenesin and alcohol 3 to 4%. pH 2.3 to 3. Store in airtight containers.

Guaifenesin Tablets (U.S.P.). Tablets containing guaiphenesin. Store in airtight containers.

Guaiphenesin Linctuses. (1) *Lemon-flavoured.* Guaiphenesin 2 g , glycerol 10 ml , chloroform spirit 10 ml , menthol 10 mg , compound tartrazine solution 0.2 ml , water 10 ml , modified lemon syrup to 100 ml .

(2) *Tolu-flavoured.* Guaiphenesin 2 g , glycerol 10 ml , chloroform spirit 10 ml , menthol 10 mg , amaranth solution 1 ml , tolu solution 10 ml , invert syrup 20 ml , syrup to 100 ml .

Modified lemon syrup contains lemon spirit 0.5 ml , citric acid monohydrate 2.5 g , invert syrup 20 ml , syrup to 100 ml .

Both lemon-flavoured and tolu-flavoured guaiphenesin linctuses remained stable for 6 months when stored at temperatures from -5° to 37° .— Pharm. Soc. Lab. Rep. No. P/65/21, 1965. See also G. Smith, *Pharm. J.*, 1966, 1, 165.

Proprietary Preparations

Dimotane Expectorant (Robins, UK). Contains in each 5 ml guaiphenesin 100 mg , brompheniramine maleate 2 mg , phenylephrine hydrochloride 5 mg , and phenylpropranolamine hydrochloride 5 mg (suggested diluent, syrup). **Dimotane Expectorant DC** contains in addition hydrocodone tartrate 1.8 mg in each 5 ml . *Dose.* 5 to 10 ml four times daily; children, 1 to 3 years, 1 to 2.5 ml ; 3 to 6 years, 2.5 to 5 ml ; 6 to 12 years, 5 ml .

Dimotane with Codeine (Robins, UK). Contains in each 5 ml guaiphenesin 100 mg , codeine phosphate 10 mg , brompheniramine maleate 2 mg , phenylephrine hydrochloride 5 mg , and phenylpropranolamine hydrochloride 5 mg (suggested diluent, syrup). For cough. *Dose.* 5 to 10 ml four times daily.

Dimotane with Codeine Paediatric (Robins, UK). Contains in each 5 ml guaiphenesin 50 mg , codeine phosphate 3 mg , brompheniramine maleate 1 mg , phenylephrine hydrochloride 2.5 mg , and phenylpropranolamine hydrochloride 2.5 mg (suggested diluent, syrup). *Dose.* 3 to 6 years, 5 ml four times daily; 6 to 12 years, 5 to 10 ml .

Exyphen (Norton, UK; Vestric, UK). An elixir containing in each 5 ml guaiphenesin 80 mg , brompheniramine maleate 2 mg , phenylephrine hydrochloride 4.75 mg , and phenylpropranolamine hydrochloride 5 mg . For cough. *Dose.* 5 to 10 ml four times daily; children, 2.5 to 5 ml three or four times daily.

Noradran Bronchial Syrup (Norma, UK; Farillon, UK). Contains in each 5 ml guaiphenesin 25 mg , diphenhydramine hydrochloride 5 mg , diprophyllyne 50 mg , and ephedrine hydrochloride 7.5 mg . *Dose.* 10 ml every 4 hours; children over 5 years, 5 ml .

Pholcomed Expectorant (formerly known as Pulmodrine Expectorant) (Medo Chemicals, UK). Contains in each 5 ml guaiphenesin 62.5 mg and methylephedrine hydrochloride $62.5 \mu\text{g}$. *Dose.* 10 to 20 ml thrice daily; children, 2.5 to 5 ml .

Robitussin (Robins, UK). An expectorant mixture containing in each 5 ml guaiphenesin 100 mg (suggested diluent, syrup). (Also available as Robitussin in Austral., Canad., Ital.)

Robitussin AC (Robins, UK). Contains in each 5 ml guaiphenesin 100 mg , codeine phosphate 10 mg , and pheniramine maleate 7.5 mg (suggested diluent, syrup). For coughs. *Dose.* 5 to 10 ml four times daily; children, 6 to 12 years, 5 ml .

Juice (B.P.C. 1949). Succus Allii. Bruise garlic and express the juice; mix the marc with water and again express the liquid; repeat the operation until the volume of the mixed juice and washings is 80 ml , and add alcohol (90%) 20 ml ; allow for 14 days, and decant or filter. *Dose.* 2 to 3 ml .

Syrup (B.P.C. 1949). Syr. Allii. Garlic juice 100 g , sucrose 80 g , acetic acid (6 per cent) 20 ml , alcohol 20 ml . *Dose.* 2 to 8 ml .

Grindelia (B.P.C. 1949). Gum Plant; Gumweed; Tar

Pharmacopoeias. In Belg. and Fr. which also allow *G. robusta*, and *G. squarrosa*. Span. and Port. allow *G. robusta*; Port. also allows *G. squarrosa*.

Dried leaves and flowering tops of *Grindelia campocoma* (Compositae) containing not less than 20% of alcohol-soluble extractive. Store in a cool dry place.

Grindelia has expectorant properties and has been stated to exert a spasmolytic effect. It has been used as an extract or a tincture in the treatment of asthma and bronchitis. Large doses sometimes cause renal disturbances. Its nauseous taste may be masked with chloroform or glycerol.

Preparations

Liquid Extract (B.P.C. 1949). Ext. Grindelia. *Grindelia* 100 g is exhausted by percolation with alcohol (90%), the alcohol is removed by distillation, and the residue is dissolved in water 50 ml to which 10 g of sodium bicarbonate has previously been added; effervescence has ceased, the solution is adjusted to 100 ml with alcohol (90%) and filtered. *Dose.* 0.6 to 2 ml .

2016-z

Guaiacol (B.P.C. 1949). Guaiacol; Methyl Catechol.

CAS — 90-05-1 (2-methoxyphenol).

Pharmacopoeias. In Arg., Fr., It., Mex., Port., Roum., and Swiss.

Colourless or almost colourless oily liquid or crystals with a penetrating aromatic odour and a caustic taste, obtained as a liquid by fractional distillation of wood-tar distillate or, usually as crystals, by synthesis.

The main constituent is 2-methoxyphenol, $C_7H_8O_2$, m.p. 124.1° . Wt per ml (liquid) about 1.22 g ; m.p. (crystals) about 28° . It tends to become brownish on exposure to light.

Soluble 1 in 80 of water; miscible with alcohol, chloroform, ether, glacial acetic acid, and fixed and volatile oils; soluble 1 in 1 of glycerol but separates out on the addition of water. Incompatible with ferric salts, sulphur, menthol, and chloral hydrate. Protect from light.

Guaiacol has disinfectant properties similar to those of creosote. It has been used as an expectorant in doses of 0.3 to 0.6 ml . Adverse effects are similar to those of Phenol, p.571.

2017-c

Guaiacol Carbonate (B.P.C. 1949). Duotal. Bis(2-methoxyphenyl) carbonate.

$C_{14}H_{16}O_4$, m.p. 274.3° .

CAS — 553-17-3.

Pharmacopoeias. In Port. and Span.

Guaiacol carbonate is the carbonic ester of guaiacol. It is a white, almost odourless, tasteless, crystalline powder. M.p. 83° to 88° . Practically insoluble in water; soluble 1 in 70 of alcohol and 1 in 20 of ether; readily soluble in chloroform; slightly soluble in glycerol and fixed oils. It is decomposed by alcoholic potassium hydroxide solution and guaiacol separates from the solution on the addition of excess acid.

Guaiacol carbonate has the actions of guaiacol but is less irritant. It has been used in doses of 0.3 to 1 g . It liberates guaiacol slowly and incompletely in the intes-

A. INGREDIENT NAME:

HYDRAZINE SULFATE

B. Chemical Name:

Hydrazinium Sulfate, Hydrazonium Sulfate

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specifications)</i>	<i>(Results)</i>
Assay:	99.0% min.	99.3%

E. Information about how the ingredient is supplied:

White Crystalline Powder

F. Information about recognition of the substance in foreign pharmacopeias:

USP 23, Indian Pharmacopeia 3rd Ed.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Gold, J. Use of Hydrazine Sulfate in terminal and Preterminal Cancer patients: results of investigational new drug (IND) study in 84 valuable patients. *Oncology*. 1975; 32(1): 1-10

Chlebowski, R. T., Bulcavage, L., and Grosvenor, M. Hydrazine Sulfate in Cancer patients with weight loss. A placebo-controlled clinical experience. *Cancer*. 1987; 59(3): 406-410.

Bairam, A. Theophylline versus caffeine: comparative effects in treatment of idiopathic apnea in the preterm infant. *J. Pediatr*. 1987; 110:636.

Eisenberg, M. G. and Kang, N. Stability of citrated caffeine solutions for injectable and external use. *Am. J. Hosp. Pharm.* 1984;41:2405.

H. Information about dosage forms used:

I. Information about strength:

60mg, 3 times/d

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 254°

Oxidizing Agents

Bases

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

50-1876

49320

PRODUCT: HYDRAZINE SULFATE REAGENT
RELEASE #: N

LOT #: L609141

GRADE: A.C.S.
CODE: G61024

	<u>SPECIFICATIONS</u>	<u>RESULT</u>
1. DESCRIPTION	<u>WHITE CRYSTALLINE POWDER</u> E	CONFORMS
2. Identification	To pass test	Passes test
3. Residue on Ignition	0.05% max.	0.01%
4. Insoluble matter	0.005% max.	0.0025%
5. <u>Assay</u>	<u>99.0% min.</u>	<u>99.3%</u> D
6. Heavy Metals	0.002% max.	< 0.001%
7. Chloride	0.005% max.	0.002%
8. Iron	0.001% max.	< 0.0003%

ATTENTION: TONY HATCHETT

Date : 04/09/97

10690

Prepared by : A. HAZARI

Approved by :  4/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: HYDRAZINE SULFATE A.C.S. REAGENT

MANUFACTURE LOT NO.: 609141

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

WHITE TO ORTHORHOMBIC CRYSTALS. GLASS-LIKE PLATES OR PRISMS.

2) SOLUBILITY.:

SOLUBLE IN ABOUT 33 PARTS OF COLD WATER; FREELY SOLUBLE IN HOT WATER. INSOLUBLE IN ALCOHOL.

3) MELTING POINT.:

MELTS AT ABOUT 254 degree. K

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

A) A SOLUTION RESPONDS TO THE TESTS FOR SULFATE.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____



Fisher Scientific



Use your web browser's "Back" key to return to previous topic.

Hydrazine Sulfate

**** MATERIAL SAFETY DATA SHEET ****

Hydrazine Sulfate

11070

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: Hydrazine Sulfate

Catalog Numbers:

H320 500, H320-500, H320500

Synonyms:

Diamine Sulfate; Hydrazine Monosulfate; Hydrazinium Sulfate.

Company Identification: Fisher Scientific
1 Reagent Lane
Fairlawn, NJ 07410

For information, call: 201-796-7100

Emergency Number: 201-796-7100

For CHEMTREC assistance, call: 800-424-9300

For International CHEMTREC assistance, call: 703-527-3887

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
10034-93-2	HYDRAZINE SULFATE	>99	233-110-4

Hazard Symbols: T

Risk Phrases: 23/24/25 43 45

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: white.

Danger! Corrosive. Carcinogen. May be harmful if swallowed.

Sensitizer. May cause lung damage. May cause severe eye irritation and possible injury. May cause liver and kidney damage. May cause severe skin irritation and possible burns. May cause severe respiratory and digestive tract irritation with possible burns. May cause cancer based on animal studies. Material is shock sensitive and potentially explosive.

Target Organs: Blood, kidneys, central nervous system, liver.

Potential Health Effects

Eye:

Contact with eyes may cause severe irritation, and possible eye burns. May cause eye injury.

Skin:

May cause skin sensitization, an allergic reaction, which becomes

evident upon re-exposure to this material. May cause severe skin irritation with possible burns, especially if skin is wet or moist.

Ingestion:

May cause liver and kidney damage. May cause severe digestive tract irritation with abdominal pain, nausea, vomiting and diarrhea. May cause corrosion and permanent tissue destruction of the esophagus and digestive tract. Exposure may cause anemia and other blood abnormalities. May be harmful if swallowed.

Inhalation:

Irritation may lead to chemical pneumonitis and pulmonary edema. May cause liver and kidney damage. May cause severe irritation of the upper respiratory tract with pain, burns, and inflammation. May cause effects similar to those described for ingestion.

Chronic:

Prolonged or repeated skin contact may cause sensitization dermatitis and possible destruction and/or ulceration. May cause liver and kidney damage. May cause cancer according to animal studies. May cause digestive tract disturbances.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:

Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.

Skin:

Get medical aid immediately. Immediately flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:

Do NOT induce vomiting. If victim is conscious and alert, give 2-4 cupfuls of milk or water. Get medical aid immediately.

Inhalation:

Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Notes to Physician:

Treat symptomatically and supportively.

Antidote:

No specific antidote exists.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:

As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Dusts at sufficient concentrations can form explosive mixtures with air. Combustion generates toxic fumes. Material is shock sensitive and potentially explosive. Greatly increases the burning rate of combustible materials. Violently decomposes when heated under confinement.

Extinguishing Media:

For small fires, use water spray, dry chemical, carbon dioxide or chemical foam.

Autoignition Temperature: Not applicable.

Flash Point: Not applicable.

NFPA Rating: Not published.

Explosion Limits, Lower: Not available.

Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:

Sweep up, then place into a suitable container for disposal. Avoid generating dusty conditions.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:

Wash thoroughly after handling. Remove contaminated clothing and

wash before reuse. Use with adequate ventilation. Minimize dust generation and accumulation. May form flammable dust-air mixtures. Loosen closure cautiously before opening. Do not get on skin and clothing. Empty containers retain product residue, (liquid and/or vapor), and can be dangerous. Do not ingest or inhale. Avoid mechanical shock and friction. Do not pressurize, cut, weld, braze, solder, drill, grind, or expose empty containers to heat, sparks or open flames.

Storage:

Keep away from heat, sparks, and flame. Do not store near combustible materials. Store in a tightly closed container. Store in a cool, dry, well-ventilated area away from incompatible substances.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:

Use process enclosure, local exhaust ventilation, or other engineering controls to control airborne levels.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
HYDRAZINE SULFATE	none listed	none listed	none listed

OSHA Vacated PELs:

HYDRAZINE SULFATE:

No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:

Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:

Wear appropriate protective gloves to prevent skin exposure.

Clothing:

Wear appropriate protective clothing to prevent skin exposure.

Respirators:

Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State: Solid
 Appearance: white
 Odor: None reported.
 pH: 1.3 (0.2M solution)
 Vapor Pressure: Negligible.
 Vapor Density: Not applicable.
 Evaporation Rate: Negligible.
 Viscosity: Not available.
 Boiling Point: Not available.
 Freezing/Melting Point: 489 deg F
 Decomposition Temperature: Not available.
 Solubility: Soluble in water.
 Specific Gravity/Density: 1.4 (water=1)
 Molecular Formula: H4N2.H2SO4
 Molecular Weight: 130.12

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:

Stable under normal temperatures and pressures. Substance is shock sensitive and thermally unstable.

Conditions to Avoid:

Mechanical shock, incompatible materials, temperatures above 160°C.

Incompatibilities with Other Materials:

K Oxidizing agents, combustible materials, sodium amide.

Hazardous Decomposition Products:

Nitrogen oxides, carbon monoxide, oxides of sulfur, carbon dioxide.

Hazardous Polymerization: Has not been reported.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:

CAS# 10034-93-2: MV9625000

LD50/LC50:

CAS# 10034-93-2: Oral, mouse: LD50 = 740 mg/kg; Oral, rat: LD50 = 601 mg/kg.

Carcinogenicity:

HYDRAZINE SULFATE -

California: carcinogen

NTP: Suspect carcinogen

OSHA: Possible Select carcinogen

Epidemiology:

Oral and intraperitoneal administration of hydrazine salts to animals have produced lung and liver carcinomas.

Teratogenicity:

No information available.

Reproductive Effects:

No information available.

Neurotoxicity:

No information available.

Mutagenicity:

Please refer to RTECS# MV9625000 for specific information.

Other Studies:

Skin irritation, guinea pig: slight. Eye irritation, rabbit: severe.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:

No information available.

Environmental Fate:

No information reported.

Physical/Chemical:

No information available.

Other:

None.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.

RCRA D-Series Maximum Concentration of Contaminants: Not listed.

RCRA D-Series Chronic Toxicity Reference Levels: Not listed.

RCRA F-Series: Not listed.

RCRA P-Series: Not listed.

RCRA U-Series: Not listed.

Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT

Shipping Name: CORROSIVE SOLID, ACIDIC, INORGANIC, N.O.S.
(HYDRAZINE SULFATE)

Hazard Class: 8

UN Number: UN3260

Packing Group: II

IMO

No information available.

IATA

No information available.

RID/ADR

No information available.

Canadian TDG

Shipping Name: CORROSIVE SOLIDS NOS (HYDRAZINE SULFATE)

Hazard Class: 8(9.2)

UN Number: UN1759

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA

CAS# 10034-93-2 is listed on the TSCA inventory.

Health & Safety Reporting List

None of the chemicals are on the Health & Safety Reporting List.

Chemical Test Rules

None of the chemicals in this product are under a Chemical Test Rule.

Section 12b

None of the chemicals are listed under TSCA Section 12b.

TSCA Significant New Use Rule

None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)

None of the chemicals in this material have an RQ.

Section 302 (TPQ)

None of the chemicals in this product have a TPQ.

SARA Codes

CAS # 10034-93-2: acute, chronic, reactive.

Section 313

This material contains HYDRAZINE SULFATE (CAS# 10034-93-2, >99%), which is subject to the reporting requirements of Section 313 of SARA Title III and 40 CFR Part 373.

Clean Air Act:

This material does not contain any hazardous air pollutants.

This material does not contain any Class 1 Ozone depletors.

This material does not contain any Class 2 Ozone depletors.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.

None of the chemicals in this product are listed as Priority Pollutants under the CWA.

None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

HYDRAZINE SULFATE can be found on the following state right to know lists: New Jersey, Florida, Pennsylvania, Minnesota, Massachusetts.

The following statement(s) is(are) made in order to comply with the California Safe Drinking Water Act:

WARNING: This product contains HYDRAZINE SULFATE, a chemical known to the state of California to cause cancer.

California No Significant Risk Level:

CAS# 10034-93-2: no significant risk level = 0.2 ug/day

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: T

Risk Phrases:

R 23/24/25 Toxic by inhalation, in contact with skin and if swallowed.

R 43 May cause sensitization by skin contact.

R 45 May cause cancer.

Safety Phrases:

S 44 If you feel unwell, seek medical advice (show the label where possible).

S 53 Avoid exposure - obtain special instructions before use.

WGK (Water Danger/Protection)

CAS# 10034-93-2:

Canada

CAS# 10034-93-2 is listed on Canada's DSL/NDSL List.

This product has a WHMIS classification of D2A, E.

CAS# 10034-93-2 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Spectral purity—Measure in a 1-cm cell at 300 nm, with a suitable spectrophotometer, against air as the blank: its absorbance is not more than 0.08.

Hexanes (suitable for use in ultraviolet spectrophotometry); usually a mixture of several isomers of hexane (C₆H₁₄), predominantly *n*-hexane, and methylcyclopentane (C₆H₁₂)—Use ACS reagent grade.

Hexanitrodiphenylamine (Dipicrylamine), C₁₂H₅N₇O₁₂—**439.21**—Yellow-gold powder or prisms. *Explosive*. Usually contains about 15% of water as a safety precaution. Insoluble in water, in alcohol, in acetone, and in ether; soluble in glacial acetic acid and in alkalis.

Water, Method I (921): not more than 16%.

Hexanophenone, C₁₂H₁₆O—**176.26**—Yellow liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* (621)) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 30-m × 0.25-mm capillary column coated with a 1-μm layer of phase G3; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the C₁₂H₁₆O peak is not less than 98% of the total peak area.

Refractive index (831): 1.511 ± 0.002 at 20°.

Hexokinase and Glucose-6-phosphate Dehydrogenase Suspension—Use a suitable grade.¹

Suitability—When used in the assay of lactulose, determine that a suitable absorbance-versus-concentration slope is obtained, using USP Lactulose RS, the reagent blank absorbance being not more than 0.020.

Histamine Dihydrochloride, C₇H₉N₃·2HCl—**184.07**—Use USP Histamine Dihydrochloride RS.

Hydrazine Hydrate, 85% in Water, (NH₂)₂·H₂O—**50.06**—Colorless liquid.

Assay—Transfer 600 mg, accurately weighed, to a 100-mL volumetric flask. Dilute with water to volume, and mix. Pipet 10 mL into a suitable beaker, add 1.0 g of sodium bicarbonate and 50.0 mL of 0.1 *N* iodine VS. Titrate the excess iodine with 0.1 *N* sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* iodine is equivalent to 12.52 mg of (NH₂)₂·H₂O. Not less than 83% is found.

Hydrazine Dihydrochloride, (NH₂)₂·2HCl—**104.97**—White powder.

Assay—Dissolve about 34 mg, accurately weighed, in 50 mL of water. Add carefully while stirring, 1 g of sodium bicarbonate. [*Caution—There may be a rapid evolution of carbon dioxide.*] Titrate with 0.1 *N* iodine solution, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 *N* iodine solution is equivalent to 2.63 mg of (NH₂)₂·2HCl. Not less than 98% is found.

Hydrazine Sulfate, (NH₂)₂·H₂SO₄—**130.13**—Use ACS reagent grade.

Hydriodic Acid, HI—**127.91**—Use ACS reagent grade (containing not less than 47.0% of HI).

NOTE—For *Methoxy Determination* (see (431)), use hydriodic acid that is labeled “for alkoxyl determination,” or that is purified as directed under *Methoxy Determination* (431). Use this grade also for alkoxyl determinations in assays in the individual monographs.

Hydrochloric Acid, HCl—**36.46**—Use ACS reagent grade.

Hydrochloric Acid, Diluted (10 percent)—Prepare by mixing 226 mL of hydrochloric acid with sufficient water to make 1000 mL.

Hydrofluoric Acid, HF—**20.01**—Use ACS reagent grade.

Hydrogen Peroxide, 30 Percent, H₂O₂—**34.01**—Use ACS reagent grade.

Hydrogen Peroxide Solution—Use *Hydrogen Peroxide Topical Solution*.

Hydrogen Sulfide, H₂S—**34.08**—Colorless, poisonous gas, heavier than air. Soluble in water. Is generated by treating fer-

rous sulfide with diluted sulfuric or diluted hydrochloric acid. Other sulfides yielding hydrogen sulfide with diluted acids may be used. Is also available in compressed form in cylinders.

Hydrogen Sulfide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator, the latter consisting of a suitable lead salt.

NOTE—A suitable detector tube that conforms to the monograph specification is available from National Draeger, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number 6719001, Measuring Range 1 to 20 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices*.

Hydroquinone, C₆H₄(OH)₂—**110.11**—Fine, colorless or white, needle crystals. Darkens on exposure to air and light. Soluble in water, in alcohol, and in ether.

Assay—Weigh accurately about 250 mg, and dissolve in a mixture of 100 mL of water and 10 mL of 0.1 *N* sulfuric acid in a 250-mL conical flask. Add 3 drops of a 1 in 100 solution of diphenylamine in sulfuric acid, and titrate with 0.1 *N* ceric sulfate VS until the solution is red-violet in color. Each mL of 0.1 *N* ceric sulfate is equivalent to 5.506 mg of C₆H₄(OH)₂. Not less than 99% is found.

Melting range (741): between 172° and 174°.

3-Hydroxyacetophenone, C₈H₈O₂—**136.15**—Light brown powder chips and chunks. Melts at about 96°. Sparingly soluble in chloroform, yielding a clear, light yellow solution.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* (621)) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G1; the detector and the injection port temperature are maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280° and held at that temperature for 10 minutes. The area of the main peak is not less than 97% of the total peak area.

4-Hydroxyacetophenone, HOC₆H₄COCH₃—**136.15**—Gray powder, melting at about 109°.

***p*-Hydroxybenzoic Acid**, C₇H₆O₃—**138.12**—White crystals.

Assay—Transfer about 700 mg, accurately weighed, to a suitable container, and dissolve in 50 mL of acetone. Add 100 mL of water, mix, and titrate with 0.5 *N* sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 *N* sodium hydroxide is equivalent to 69.06 mg of C₇H₆O₃: not less than 97% is found.

Melting range (741): over a range of 2° that includes 216°.

4-Hydroxybenzoic Acid Isopropyl Ester, HOC₆H₄COOCH(CH₃)₂—**180.20**—Use a suitable grade.³²

Melting range (741): between 84° and 87°.

1-Hydroxybenzotriazole Hydrate, C₆H₅N₃O·*x*H₂O—**135.13** (anhydrous)—White crystalline powder. Sparingly soluble in alcohol yielding a clear, pale yellow solution.

2-Hydroxybenzyl Alcohol, C₇H₈O₂—**124.14**—Off-white flakes. Very soluble in alcohol, in chloroform, and in ether; soluble in 15 parts water and in benzene.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* (621)), equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-μm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the C₇H₈O₂ peak is not less than 99% of the total peak area.

Melting range (741): between 83° and 85°.

4-Hydroxyisophthalic Acid, C₈H₆O₄—**182.13**—Colorless branched needles. Freely soluble in alcohol and in ether.

Melting range (741): between 314° and 315°, with decomposition.

(C) Government of India
Ministry of Health & Family Welfare

Pharmacopoeia of India

(The Indian Pharmacopoeia)

Volume—II
(Q—Z & Appendices)

Third Edition



PUBLISHED BY THE CONTROLLER OF PUBLICATIONS, DELHI

1985

A fraction from petroleum containing about 90 per cent of *n*-hexane.

DESCRIPTION - Colourless, mobile, highly flammable liquid.

DISTILLATION RANGE - Not less than 95 per cent, distils between 67° and 70°, Appendix 5.3.

WT. PER ML - At 20°, 0.670 to 0.677 g, Appendix 5.19.

NON-VOLATILE MATTER - When evaporated on a water-bath and dried to constant weight at 105°, leaves not more than 0.01 per cent w/v of residue.

Histamine Acid Phosphate

Of the Indian Pharmacopoeia.

Histamine Dihydrochloride : $C_5H_9N_3 \cdot 2HCl = 184.07$

DESCRIPTION - White crystalline powder.

SOLUBILITY - Freely soluble in *water* and in *methyl alcohol*; soluble in *alcohol*.

MELTING POINT - About 250°, Appendix 5.11.

DL-Histidine Monohydrochloride

$N \cdot CH \cdot NH \cdot CH \cdot C \cdot CH_2 \cdot CH(NH_2) \cdot COOH \cdot HCl = 191.62$

Contains not less than 99.0 per cent of $C_6H_9N_3O_2 \cdot HCl$, calculated with reference to the substance dried to constant weight at 105°.

DESCRIPTION - White, crystalline powder.

SOLUBILITY - Soluble in *water*.

LOSS ON DRYING - Loses not more than 9.0 per cent of its weight, when dried to constant weight at 105°, Appendix 5.8.

SULPHATED ASH - Not more than 0.1 per cent, Appendix 3.2.7.

ASSAY - Carry out the method for the *determination of nitrogen, Method A*, Appendix 3.3.5, using 0.15 g and 7 ml of *nitrogen-free sulphuric acid*. Each ml of 0.1N *sulphuric acid* is equivalent to 0.00639 g of $C_6H_9N_3O_2 \cdot HCl$.

Holmium Oxide : $Ho_2O_3 = 377.86$

DESCRIPTION - A yellow solid.

SOLUBILITY - Practically insoluble in *water*.

Holmium Perchlorate Solution

A 5 per cent w/v solution of *holmium oxide* in 1.4 M *perchloric acid*.

Hydrazine Hydrate : $NH_2 \cdot NH_2 \cdot H_2O = 50.06$

DESCRIPTION - Clear, colourless liquid with an ammoniacal odour.

SOLUBILITY - Miscible with *water*.

WT. PER ML - 1.03 g, Appendix 5.19.

Hydrazine Sulphate : $NH_2 \cdot NH_2 \cdot H_2SO_4 = 130.12$

Contains not less than 99.0 per cent of $N_2H_6SO_4$.

DESCRIPTION - White, crystalline powder.

SOLUBILITY - Freely soluble in *water*; practically insoluble in *alcohol*.

MELTING POINT - About 254°, Appendix 5.11.

CHLORIDE - 1 g complies with the *limit test for chlorides*, Appendix 3.2.2.

IRON - 1 g complies with the *limit test for iron*, Appendix 3.2.5.

SULPHATED ASH - Not more than 0.05 per cent, Appendix 3.2.7.

ASSAY - Weigh accurately about 0.1 g and dissolve in 20 ml of *water*. Add 3 g of *sodium bicarbonate* and titrate with 0.1N *iodine*, using *starch solution* as indicator. Each ml of 0.1N *iodine* is equivalent to 0.003253 g of $N_2H_6SO_4$.

Hydriodic Acid : $HI = 127.91$

Constant-boiling hydriodic acid contains 55.0 per cent w/w of HI (limits, 54.0 to 56.0).

DESCRIPTION - Almost colourless liquid when freshly made, but rapidly becoming yellow to brown owing to the liberation of iodine.

SOLUBILITY - Miscible in all proportions with *water* and with *alcohol*.

BOILING POINT - About 127°, Appendix 5.3.

WT. PER ML - At 20°, about 1.7 g, Appendix 5.19.

CHLORIDE AND BROMIDE - To 0.2 ml add 15 ml of *water*, 50 mg of *sodium sulphate*, 5 ml of *dilute ammonia solution* and 20 ml of 0.1N *silver nitrate*, shake and filter; to the filtrate add 10 ml of *dilute nitric acid*. The opalescence produced is not greater than the standard opalescence obtained in the *limit test for chlorides*, Appendix 3.2.2.

SULPHATE - Dilute 1 ml with 50 ml of *water* and add 1 ml of *barium chloride solution*. The turbidity produced should not be greater than the standard opalescence obtained in the *limit test for sulphates*, Appendix 3.2.8.

NON-VOLATILE MATTER - When evaporated on a water-bath, and dried to constant weight at 105°, leaves not more than 0.5 per cent w/w of residue.

ASSAY - Weigh accurately about 0.6 g into a stoppered flask containing about 10 ml of *water*, dilute with 25 ml of *water* and titrate the free iodine with 0.1N *sodium thio-*

TABLE 2

Size No.	Kinematic Viscosity Range (Centistokes)	Volume Bulb C (ml) ($\pm 5\%$)	Inside Diameter of Tube N (mm)	Inside Diameter of Tube R (mm) ($\pm 2\%$)
1	3.5* to 10	0.64	5.6	2.8 to 3.2
1A	5 to 30	0.84	5.6	2.8 to 3.2
2	20 to 100	1.15	5.6	2.8 to 3.2
2A	60 to 300	1.51	5.6	2.8 to 3.2
3	200 to 1100	2.06	5.6	3.7 to 4.3
3A	600 to 3000	2.74	5.6	4.6 to 5.4
4	2000 to 10,000	3.70	5.6	4.6 to 5.4
4A	6000 to 30,000	4.97	5.6	5.6 to 6.4
5	20,000 to 100,000	6.76	5.6	6.8 to 7.5

350 minimum flow time; 200 minimum flow time for all other sizes

any time while the flow time is being measured, the determination must be repeated.

Calculate the kinematic viscosity in centistokes (V) from the equation:

$$v = Ct.$$

where

t = time in seconds for the meniscus to fall from E to F

C = the constant of the viscometer, determined by observations on a liquid of known viscosity.

Method C : (Using the Rotating Viscometer)

The rotating viscometer measures the shearing forces in a liquid medium placed between two coaxial cylinders one of which is driven by a motor and the other is caused to revolve by the rotation of the first. Under these conditions, the viscosity becomes a measurement of the angle of deflection of the cylinder caused to revolve, expressed in newton metres.

Method—Operate the Rotating Viscometer in accordance with the manufacturer's instructions and carry out the determination of viscosity of the liquid being examined, at the temperature and angular velocity or shear rate specified in the individual monograph.

Calculate the dynamic viscosity (η) in centipoises.

5.19 WEIGHT PER MILLILITRE AND SPECIFIC GRAVITY

Weight per Millilitre

The weight per millilitre of a liquid is the weight in g of

1 ml of a liquid when weighed in air at 25°, unless otherwise specified.

Method : Select a thoroughly clean and dry pycnometer. Calibrate the pycnometer by filling it with recently boiled and cooled *water* at 25° and weighing the contents. Assuming that the weight of 1 ml of *water* at 25° when weighed in air of density 0.0012 g per ml, is 0.99602 g, calculate the capacity of the pycnometer. (Ordinary deviations in the density of air from the value given do not affect the result of a determination significantly). Adjust the temperature of the substance to be examined, to about 20° and fill the pycnometer with it. Adjust the temperature of the filled pycnometer to 25°, remove any excess of the substance and weigh. Subtract the tare weight of the pycnometer from the filled weight of the pycnometer. Determine the weight per millilitre by dividing the weight in air, expressed in g, of the quantity of liquid which fills the pycnometer at the specified temperature, by the capacity expressed in ml, of the pycnometer at the same temperature.

Specific Gravity

The specific gravity of a liquid is the weight of a given volume of the liquid at 25° (unless otherwise specified) compared with the weight of an equal volume of *water* at the same temperature, all weighings being taken in air.

Method : Proceed as described under **Wt. per ml.** Obtain the specific gravity of the liquid by dividing the weight of the liquid contained in the pycnometer by the weight of *water* contained, both determined at 25° unless otherwise directed in the individual monograph.

Hydrazine Sulphate. $H_2N_2O_2S=130.1$

CAS — 302-01-2 (hydrazine); 10034-93-2 (sulphate).

Crystals. Soluble 1 in about 33 of water, freely soluble in hot water; practically insoluble in alcohol. A 0.2M solution in water has a pH of 1.3.

Hydrazine sulphate is employed in various industrial processes. It is used in the preparation of hydrazine hydrate which is applied after a solution of platinum chloride for corneal tattooing (see Chloroplatinic Acid, p.1693).

An account of the successful treatment of industrial hydrazine poisoning with pyridoxine.— J. K. Kirkin *et al.*, *New Engl. J. Med.*, 1976, 294, 938.A report of fatal choroidal melanoma in a worker who had been exposed to hydrazine for 6 years.— D. M. Albert and C. A. Puliafito (letter), *New Engl. J. Med.*, 1977, 296, 634.The use of hydrazine sulphate by a laboratory worker was associated with the development of a syndrome similar to systemic lupus erythematosus.— P. J. Durant and R. A. Harris (letter), *New Engl. J. Med.*, 1980, 303, 584.A discussion of hydrazine sulphate as an antineoplastic agent.— W. Regelson, *J. Am. med. Ass.*, 1980, 243, 337.

12832-k

Hydrogen Sulphide. Sulphuretted Hydrogen. $H_2S=34.08$.

CAS — 7783-06-4.

A colourless inflammable gas with a characteristic odour; the intensity of the smell gives no indication of concentration.

Adverse Effects. Hydrogen sulphide poisoning is a common industrial hazard and is encountered in such places as chemical works, mines, sewage works, and stores of decomposing protein; concentrations of 0.1 to 0.2% in the atmosphere may be fatal in a few minutes. Pulmonary irritation, coma, and respiratory failure usually occur in acute poisoning; prolonged exposure to low concentrations may give rise to severe conjunctivitis with photophobia and corneal opacity, irritation of the respiratory tract, rhinitis, bronchitis, stomatitis, pharyngitis, digestive disturbances, headache, lassitude, and skin rashes. There are some similarities to poisoning with cyanides.A discussion of poisoning by hydrogen sulphide — *Lancet*, 1978, 1, 28. Comments.— A. Downie (letter), *ibid.*, 1978, 118, 775; W. W. Burnett and E. G. King (letter), *ibid.*, 776; J. Am. med. Ass., 1978, 239, 1374.Concentrations of about 200 ppm caused irritation of the respiratory tract and, on prolonged exposure, pulmonary oedema. Toxicity to the CNS could occur suddenly at concentrations in excess of 500 ppm and immediate death might follow concentrations in excess of 1000 ppm. Irritation to the eyes occurred at concentrations of less than 50 ppm — *Methods for the Detection of Toxic Substances in Air. Hydrogen Sulphide*. London, HM Stationery Office, 1969.Further references. W. W. Burnett *et al.*, *Can. med. Ass. J.*, 1977, 117, 1277; R. P. Smith (letter), *ibid.*, 1978, 118, 775; W. W. Burnett and E. G. King (letter), *ibid.*, 776; J. Am. med. Ass., 1978, 239, 1374.**Treatment of Adverse Effects.** After exposure to hydrogen sulphide place the patient in fresh air, give inhalations of oxygen and, if necessary, assist the respiration. Antibiotics may be necessary if pulmonary infection occurs. The conjunctival sacs should be carefully washed out if eye irritation is severe.

In severe poisoning, amyl nitrite inhalation and sodium nitrite by intravenous injection have been suggested.

A brief review of the management of sulphide poisoning — R. P. Smith and R. E. Gosselin, *A Rev. Pharmac. & Toxic.*, 1976, 16, 189.

The successful treatment of a 47-year-old man with hydrogen sulphide poisoning using oxygen, amyl nitrite inhalations for 30 seconds out of each minute for

5 minutes, and then sodium nitrite 300 mg intravenously for 3 minutes. Treatment was aimed at producing methaemoglobinemia to inactivate the sulphide. In addition he received sodium thiosulphate 12.5 g by intravenous injection — R. J. Stine *et al.*, *Ann. intern. Med.*, 1976, 85, 756.Further references: R. P. Smith and R. E. Gosselin, *J. occup. Med.*, 1979, 21, 93.**Uses.** Hydrogen sulphide is widely employed in many industrial processes.

12833-a

Hydroxyestrone Diacetate. 16 α -Hydroxyestrone Diacetate. 3,16 α -Dihydroxyestra-1,3,5(10)-trien-17-one diacetate. $C_{27}H_{26}O_5=370.4$.

CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (diacetate).

Hydroxyestrone diacetate is a derivative of oestrone. It is claimed to have minimal systemic oestrogenic effects when given by mouth but to retain effects on the vaginal mucosa. It is used in the treatment of vaginitis and associated disorders.

Proprietary Names

Colpoginon (Boizot, Spain); Colpogynon (Laboratories de l'Hepatorol, Switz.); Colpormon (Millet, Arg.; Anphar-Rolland, Fr.).

12834-t

Hydroxyethylpromethazine Chloride.

(2-Hydroxyethyl)dimethyl[1-methyl-2-(phenothiazin-10-yl)ethyl]ammonium chloride.

 $C_{19}H_{25}ClN_2OS=364.9$.

CAS — 7647-63-4 (hydroxyethylpromethazine); 2090-54-2 (chloride).

Hydroxyethylpromethazine chloride is an antihistamine.

Proprietary Names

Aprobit (Recip. Swed.).

12835-x

Hydroxymethylnicotinamide. Nicotinylmethylamide; N-Hydroxymethylnicotinamide. N-Hydroxymethylpyridine-3-carboxamide. $C_7H_8N_2O_2=152.2$.

CAS — 3569-99-1.

Crystals. M.p. 141° to 142°. Sparingly soluble in water and alcohol; freely soluble in hot water and alcohol.

Hydroxymethylnicotinamide is a choleric and has been used in the treatment of various disorders of the gall-bladder.

Proprietary Names

Bilamid (Cilag, Ger.; Bracco, Ital.; Cilag-Chemie, Switz.); Bilamide (Cilag-Chemie, Belg.); Biloide (Labatec-Pharma, Switz.).

12836-r

5-Hydroxytryptophan. 5-HTP; Ro-0783/B. 2-Amino-3-(5-hydroxy-1H-indol-3-yl)propionic acid. $C_{11}H_{12}N_2O_3=220.2$.

CAS — 56-69-9.

NOTE. The form of 5-hydroxytryptophan used clinically is generally the L-form.

5-Hydroxytryptophan is a precursor of serotonin (see p.1753) and has been used clinically in attempts to treat disorders believed to be associated with serotonin deficiency.

Changes in mood, mostly elevation, were observed in 7 neurological patients without affective disorders and 1 healthy subject given L-5-hydroxytryptophan 100 to 300 mg by intravenous infusion in sodium chloride injection. Carbidopa was also given to reduce the severity of vomiting which always occurred 30 to 90 minutes after infusion and to increase the amount of L-5-hydroxytryptophan entering the brain. Neurotoxicity occurred

with doses of 200 mg and above and included dilatation of the pupil, hyperreflexia, ataxia, and dysarthria. There was some similarity to the effects of acohol.— M. Trimbs *et al.* (letter), *Lancet*, 1975, 1, 583. See also M. H. Greenwood *et al.*, *Br. J. clin. Pharmac.*, 1975, 2, 165.Severe insomnia in a 33-year-old woman following a road accident responded to 4 consecutive nightly doses of L-5-hydroxytryptophan totalling 3 g.— M. Webb and J. G. Kirker (letter), *Lancet*, 1981, 1, 1365.**Manganese poisoning.** A beneficial response to DL-5-hydroxytryptophan, up to 3 g daily, was achieved in a patient in whom the symptoms of manganese poisoning failed to respond to levodopa.— I. Mena *et al.*, *New Engl. J. Med.*, 1970, 282, 5.**Mental disorders.** Of 107 patients with endogenous depression given L-5-hydroxytryptophan daily in divided doses by mouth for at least 5 weeks, the majority rapidly obtained a beneficial response.— I. Sano, *Munch. med. Wschr.*, 1972, 114, 1713, per *J. Am. med. Ass.*, 1972, 222, 1085. Further studies in depression: N. S. Kline *et al.*, *Am. J. Psychiat.*, 1964, 121, 379, per *Int. pharm. Abstr.*, 1965, 2, 918; T. Persson and B. E. Roos (letter), *Lancet*, 1967, 2, 987; G. d'Elia *et al.*, *Acta psychiat. scand.*, 1978, 57, 239; L. J. van Hiele, *Neuropsychobiology*, 1980, 6, 230.After oral administration of L-5-hydroxytryptophan with a peripheral decarboxylase inhibitor, mild to moderate improvement was obtained in 6 of 7 chronic undifferentiated schizophrenic patients who were resistant to phenothiazines. Of 4 chronic paranoid schizophrenic patients who were resistant to phenothiazines 2 became worse after treatment with 5-hydroxytryptophan and 1 improved. Some schizophrenic patients might have an abnormality in serotonin metabolism.— R. J. Wyatt *et al.*, *Science*, 1972, 177, 1124.Further studies in schizophrenia: V. Zarcone *et al.*, *Archs gen. Psychiat.*, 1973, 28, 843; R. J. Wyatt *et al.*, *ibid.*, 29, 597.**Myoclonus.** Comment on the use of the investigational drug L-5-hydroxytryptophan in the treatment of myoclonus and the view that in general its use should be discouraged. L-5-Hydroxytryptophan is usually effective in posthypoxic intention myoclonus, a rare condition, but may exacerbate some other myoclonic syndromes. Significant adverse effects, especially gastro-intestinal disturbances, are almost universal, even when given with a peripheral decarboxylase inhibitor such as carbidopa — R. R. Young, *J. Am. med. Ass.*, 1980, 243, 1569.L-5-Hydroxytryptophan with carbidopa was administered to 23 patients with myoclonus and 16 patients with other neurological disorders. Following administration by mouth of maximum doses of 0.4 to 2 g daily with carbidopa 100 to 300 mg daily more than 50% improvement was obtained in 11 of 18 patients with intention myoclonus due to anoxia or other brain damage; only 1 patient obtained no improvement and in 3 it was 90% or more, some patients derived sustained benefit for more than 3 years. No benefit was obtained by 2 patients with atetotic cerebral palsy, 2 with multiple sclerosis, 2 with essential tremor, 4 with cerebellar intention tremor, 1 with infantile spasms, 2 with dystonia musculorum deformans, 2 with central pain syndromes, or 3 with idiopathic epilepsy; some benefit was obtained in 1 patient with myoclonus epilepsy and in 1 of 2 patients with familial essential myoclonus. Side-effects included anorexia, nausea, diarrhoea, and occasional vomiting and were reduced by prochlorperazine or trimethobenzamide, and diphenoxylate; prior administration of carbidopa for 1 or 2 days before therapy also reduced the gastro-intestinal side-effects. During the first week of therapy 3 patients developed dyspnoea followed by hyperventilation and lightheadedness, with fainting in 1; pulmonary function tests remained normal. Varying degrees of mental stimulation occurred in 10 patients; these were reversible on dosage reduction and frequently disappeared or diminished after 4 to 6 weeks without reduction, but 2 patients required concurrent administration of perphenazine to maintain their antimyoclonic dosage. Other side-effects included mydriasis, blurring of vision, abdominal pain, and bradycardia.— M. H. Van Woert *et al.*, *New Engl. J. Med.*, 1977, 296, 70. Comment.— T. L. Munsat, *ibid.*, 101.Studies suggesting that the treatment of intention myoclonus with L-5-hydroxytryptophan and carbidopa in a 70-year-old man unmasked an abnormality in his ability to metabolise kynurenine and resulted in the development of a scleroderma-like illness — E. M. Sternberg *et al.*, *New Engl. J. Med.*, 1980, 303, 782.Further references: D. Chadwick *et al.*, *Lancet*, 1975, 2, 434; J. DeLéan and J. C. Richardson (letter), *ibid.*, 870; J. H. Growdon *et al.*, *Neurology*, Minneap., 1976, 26, 1125; W. M. Carroll and P. J. Walsh, *Br. med. J.*,

Hydrastinine

Hydrastis canadensis L. and canadine. Synonyms: Hydrastines: Hope et al. *ibid.* 1934, *Nature* 27, 1947 *Iron Letters* 22, 619 *Laworth, Pinder, J. Nature* 165, 529 *Letters* 1963, 859 *Nature* 29, 2328 (1964): 1969). Biosynthesis: 363).

Hydrastis vol. 1, G. Brauer, Ed. (Academic Press, New York, 1963) pp 469-472. Toxicity data: Witkin, *Arch. Ind. Health* 13, 34 (1956). Toxicology study: Back, Thomas, *Ann. Rev. Pharmacol.* 10, 395 (1970). Review of carcinogenicity studies: *IARC Monographs* 4, 127-136 (1974); of toxicology: R. von Burg, T. Stout, *J. Appl. Toxicol.* 11, 447-450 (1991). Books: L. F. Audrieth, B. A. Ogg, *The Chemistry of Hydrazine* (Wiley, New York, 1951); C. C. Clark, *Hydrazine* (Mathieson Chem., Baltimore, 1953). Reviews: Troyan, *Ind. Eng. Chem.* 45, 2608-2612 (1953); Zimmer, *Chem. Ztg.* 79, 599-605 (1955); Hudson et al., "Hydrazine" in *Mellor's* vol. VIII, suppl. II, *Nitrogen* (Part 2), 69-114 (1967); Jones in *Comprehensive Inorganic Chemistry* vol. 2, J. C. Bailar, Jr. et al., Eds. (Pergamon Press, Oxford, 1973) p 250-265; H. W. Schlessl in *Kirk-Othmer Encyclopedia of Chemical Technology* vol. 13 (John Wiley & Sons, New York, 4th ed., 1995) pp 560-606.

Colorless oily liq. fuming in air. Penetrating odor resembling that of ammonia. Burns with violet flame. Explodes during distn if traces of air are present, also affected by uv and metal ion catalysts. Can be stored for years if sealed in glass and kept in a cool, dark place. Flash and fire pt 126°F (52°C). Contracts on freezing. d_4^{25} 1.146; d_4^{20} 1.0253; d_4^{15} 1.024; d_4^{10} 1.011; d_4^0 1.0036; d_4^{25} 0.9955. One gallon of commercial product weighs 8.38 lbs. mp 2.0°. bp₇₆₀ 113.5°; bp₇₆₀ 56°; bp₅ 170°; bp₁₀ 200°; bp₃₀ 236°. n_D^{25} 1.46979; n_D^{20} 1.46444. Dipole moment 1.83-1.90. Dielectric constant (25°): 51.7. Latent heat of fusion (mp): 3.025 kcal/mole; latent heat of vaporization (bp): 9760 kcal/mole (calc). Crit temp 380°, crit pressure 14 atm. Diacidic base. pK_1 (25°): ~6.05. Forms salts with inorganic acids. Highly polar solvent. Powerful reducing agent. Dissolves many inorganic substances. Misc with water, methyl, ethyl, propyl, isobutyl alcohols. Forms an azeotropic mixture with water, bp₁₀₀ 120.3°, which contains 55 mole-% (68.5 weight-%) N_2H_4 . LD₅₀ in mice (mg/kg): 57 i.v.; 59 orally (Witkin). Dihydrochloride, $H_2N_2 \cdot 2HCl$, white crystalline powder, mp 198°. d 1.42. Freely sol in water, slightly in alcohol.

Caution: Potential symptoms of overexposure to hydrazine are irritation of eyes, nose and throat, temporary blindness, dizziness, nausea, dermatitis; burns skin and eyes. See *NIOSH Pocket Guide to Chemical Hazards* (DHHS NIOSH 90-117, 1990) p 124. See also Patty's *Industrial Hygiene and Toxicology*, vol. 2E, G. D. Clayton, F. E. Clayton, Eds. (John Wiley & Sons, Inc., New York, 4th ed., 1994) pp 3435-3441. Hydrazine may reasonably be anticipated to be a carcinogen. *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 231.

USE: Chemical intermediate in manuf of agricultural chemicals, spandex fibers and antioxidants. Reducing agent; organic hydrazine derivs; rocket fuel. Dihydrochloride as chlorine scavenger for HCl gas streams.

4810. Hydrazine Hydrate. $H_2N_2 \cdot O$; mol wt 50.06. H 12.08%, N 55.96%, O 31.96%. $H_2NNH_2 \cdot H_2O$. Prep'd from hydrazine sulfate by the action of NaOH, followed by distn under nitrogen.

Fuming refractive liquid, faint characteristic odor. *Potent poison! Causes delayed eye irritation.* d_4^{25} 1.03, mp -51.7° or below -65° (two eutectics). bp₇₆₀ 118-119°; bp₅ 47°. n_D^{20} 1.42842. Strong base, very corrosive, attacks glass, rubber, cork, but not stainless V₂A steel or Allegheny stainless 304 and 347. Molybdenum steels such as Allegheny stainless 316 should not be used. Very powerful reducing agent. Miscible with water and alcohol. Insol in chloroform and ether.

Mixture with methanol, *C-Stuff*. **USE:** Reducing agent, solvent for inorganic materials. Manuf "Helman" catalyst, consisting of 80% hydrazine hydrate, 19.5% ethanol, 0.5 to 0.05% copper, used to dec hydrogen peroxide in V-2 type rockets. Mixture with methanol as propellant for rocket engines.

4811. Hydrazine Sulfate, Hydrazinium sulfate; hydrazonium sulfate. $H_2N_2 \cdot O \cdot S$; mol wt 130.12. H 4.65%, N 21.53%, O 49.18%, S 24.64%. $H_2NNH_2 \cdot H_2SO_4$. Prep'd by Raschig synthesis. 2NH₃ aq - [Ca(OCl)₂]/Na₂CO₃ colloid and treatment with H₂SO₄. Starch, glue, or gelatin are used as colloids, and sodium hypochlorite may be used instead of bleaching powder. Adams, Brown, *Org. Syn.* 2, 37 (1922).

Hydrobenzoin

Audrieth, Nickles, *Inorg. Syn.* 1, 90 (1939). Industrial prep'n by the action of sodium hypochlorite on urea in the presence of NaOH: *B.I.O.S. Final Report* 369; Moncrieff, *Manuf. Chem.* 18, 177 (1947). Revised lab procedures: Pfeiffer, Simons, *Ber.* 80, 127 (1947); Adams, Brown, *Org. Syn. coll. vol. 1*, 2nd ed. (1941), p 309. Crystal structure: Nitta et al., *Acta Cryst.* 4, 289 (1951); Jönsson, Hamilton, *ibid.* 26B, 536 (1970). Review of activity and clinical studies in cancer cachexia: J. Gold, *Nutr. Cancer* 9, 59-66 (1987).

Orthorhombic crystals. Glass-like plates or prisms. d 1.378; Curtis, Jay, *J. Prakt. Chem.* 39, 39 (1889); d^7 2.016, mp 254°. Sol in about 33 parts water; freely sol in hot water. Insol in alcohol. pH of 0.2 molar aq soln 1.3.

Note: This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 231.

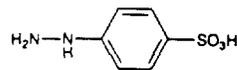
USE: In the gravimetric estimation of nickel, cobalt and cadmium; in the refining of rare metals; as antioxidant in soldering flux for light metals; as reducing agent in the analysis of minerals and slags; in separating polonium from tellurium; in tests for blood; for destroying fungi and molds; in the prep'n of hydrazine hydrate.

4812. Hydrazine Tartrate, Hydrazine acid tartrate; hydrazine hydrogen tartrate; hydrazine bitartrate. $C_4H_{10}N_2O_6$; mol wt 182.13. C 26.38%, H 5.53%, N 15.38%, O 52.71%. $H_2NNH_2 \cdot C_4H_4O_6$.

Crystals, mp 182-183°. $[\alpha]_D^{25}$ -22.5°. Soly in water at 0° about 6 g/100 ml. pH of a sat'd aq soln 3.6.

USE: In chemical deposition of metals (silvering mirrors, etc.); Owen, U.S. pat. 2,801,935 (1957 to Merck & Co.).

4813. 4-Hydrazinobenzenesulfonic Acid, p-Sulfophenylhydrazine; phenylhydrazine-p-sulfonic acid. $C_6H_7N_2O_3S$; mol wt 188.21. C 38.29%, H 4.28%, N 14.88%, O 25.50%, S 17.04%. Prep'n by sulfonation of phenylhydrazine: L. Claisen, P. Roosen, *Ann.* 278, 296 (1894); by the reduction of *p*-diazobenzenesulfonic acid: Th. Zincke, A. Kuchenbecker, *Ann.* 330, 1 (1903); L. V. Lazeeva et al., *USSR pat.* 1,057,493 (1983 to Tambov Pigment), *C.A.* 100, 138755q (1984). Used in resoln of 2-pyrazoline cmpds: M. Mukai et al., *Can. J. Chem.* 57, 360 (1979); in isoln of volatile ketones: W. Treibs, H. Röhner, *Ber.* 84, 433 (1951); in analysis of trace amounts of selenium: T. Kawashima et al., *Anal. Chim. Acta* 49, 443 (1970); *idem, ibid.* 89, 65 (1977).



Needles from water, mp 286°. Slightly sol in water, alcohol.

4814. 2-Hydrazinoethanol, 2-Hydroxyethylhydrazine; β -hydroxyethylhydrazine; Omalfora. $C_2H_7N_2O$; mol wt 76.10. C 31.57%, H 10.60%, N 36.81%, O 21.02%. $HO-CH_2CH_2NHNH_2$. Prep'n from hydrazine monohydrate and 2-chloroethanol: Gansser, *Rumf. Helv. Chim. Acta* 36, 1423 (1953); from hydrazine monohydrate and ethylene oxide: Gever, O'Keefe, U.S. pat. 2,660,607 (1953 to Eaton Labs.); from hydrazine and ethylene oxide: Brit. pat. 776,113 (1957 to Olin Mathieson).

Colorless, slightly viscous liquid. d 1.11. One gallon weighs 9.26 lbs. mp -70°. bp_{17.5} 110-130°; bp₂₅ 145-153°. Flash pt 224°F (106°C). Misc with water. Sol in the lower alcohols. Slightly sol in ether.

USE: Plant growth regulant.

4815. Hydrazoic Acid, Hydrogen azide; hydronitric acid; triazoic acid; stickstoffwasserstoffsäure (German). HN_3 ; mol wt 43.03. H 2.34%, N 97.66%. Produced by the action of sulfuric acid on sodium azide: L. F. Audrieth, C. F. Gibbs, *Inorg. Syn.* 1, 77 (1939); using stearic acid: Günther, Meyer, *Z. Elektrochem.* 41, 541 (1935). Prep'n of water and ether solns of hydrazoic acid: W. S. Frost et al., *J. Am. Chem. Soc.* 55, 3516 (1933); L. F. Audrieth, C. F. Gibbs, *loc. cit.*; P. W. Schenk in *Handbook of Preparative Inorganic Chemistry*, vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) pp 472-474. GC determ: J. M. Zehner, R.A. Simonaitis, *J. Chrom. Sci.* 14, 493 (1976). Toxic-

ity study: Graham Review of toxicology: Patty's *Industrial Clayton, F. E. C. York*, 1981) pp 2 *Comprehensive Treistry* vol. VIII, su Jones in *Compreh Bailar Jr. et al., I 276-293.*

Mobile liquid. *plosive!* mp -80 (mg/kg): 21.5 i.p.

Caution: Acute fall in blood pressu hypotension, weak USE: Industrially detonators.

4816. Hydriene-1,1',3,3'-(2H,2' 1,1',3,3'-tetraene); 322.27. C 67.09%. tion of potassium *J. Org. Chem.* 23, 1 tion of ninhydrin *Chem.* 211, 907 (19

Dihydrate, prism reddish-brown at 20 hot water; sol in M aq Na₂CO₃ solns (de blue color). Can b the addn of acid. blue color with amir

USE: Reagent for acids and similar co:

4817. Hydriodic water. Marketed ir 47%, d 1.5; 10%, d iodide gas in water sulfide according to Frykholm, *Inorg. S. Iodide.*

Colorless when fre or brown on exposu can be prevented by phorous acid (H₃PO for some time are us' be regenerated with *Jr., Inorg. Syn.* 2, 210 *air, preferably not ab.* Dissolves iodine. T bp₁₆₀ 127°, d 1.70, c acid, attacks natural

Caution: Strong ir *USE:* Reducing ag maceuticals, disinfect analytical purposes. s THERAP CAT: Expec

4818. Hydrobenz phenylethyleneglycol H 6.59%, O 14.93%. Forst, Zincke, *Ann. 1 Chem. Soc.* 91, 1390 *Soc.* 51, 2163 (1929); C. Heath, Boston, 19 Improved method for mer: Collet, *Synthesis*

11090

HYDRAZINE SULFATE



"...Since hydrazine sulfate provided relief of a wide spectrum of cancer symptoms, it may be recommended for patients with end-stage cancer."

"...virtually no significant untoward side effects..."

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GENERAL INFORMATION

Hydrazine sulfate is an anti-cachexia drug which acts to reverse the metabolic processes of debilitation and weight loss in cancer and secondarily acts to stabilize or regress tumors. Hydrazine sulfate is a monoamine oxidase (MAO) inhibitor and is incompatible with tranquilizers, barbiturates, alcohol and other central nervous system depressants. Foods high in tyramine, such as aged cheeses and fermented products, are also incompatible with MAO inhibitors. The use of tranquilizers, barbiturates and/or alcoholic beverages with hydrazine sulfate destroys the efficacy of this drug and increases patient morbidity.

The U.S. National Cancer Institute (NCI)-published studies of hydrazine sulfate (Journal of Clinical Oncology, June 1994), reported as negative, denied the use of tranquilizers, with the exception of the short-term use of prochlorperazine (Compazine). However, under pressure of an investigation of the NCI studies by the U.S. General Accounting Office ordered by Congress, the NCI in a subsequently published paper (Journal of Clinical Oncology, June 1995) admitted to the widespread use of both benzodiazepine and phenothiazine tranquilizers, which are incompatible with MAO inhibitors, in 94% of all study patients. Moreover, approximately half of these patients were given these tranquilizers on a long-term basis, and some on a continual basis. It was further admitted by the NCI that concomitant drug use (such as tranquilizers, alcohol, barbiturates, etc.) was not computerized and patient

records of such drug use were "incomplete."

There is an abundance of published, positive, peer-reviewed studies on hydrazine sulfate in the medical literature. (Abstracts of some of these published studies are given on the following pages.) These data emanate from major cancer centers both from the United States (randomized, double-blind, placebo-controlled studies and single-arm studies) and Russia (large-scale, multicentric Phase II-equivalent studies). These data indicate the therapeutic action of hydrazine sulfate to extend to all types of tumors.

Hydrazine sulfate has been demonstrated to produce only few and transient side effects. There have been no instances of bone-marrow, heart, lung, kidney or immune system toxicity, or death, reported. Hydrazine sulfate has never been demonstrated to be carcinogenic in humans.

For further information please have your HEALTH CARE PROFESSIONAL (no patients or individuals, please) call the institute.

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ARTICLES

The following is a collection of articles based on published studies on Hydrazine Sulfate. You may view the abstract by clicking on the icon to the left. If the title of an article has no hyperlink, then that article is not present on this system (you may still view the abstract).

-  ["Hydrazine Sulfate Influence on Nutritional Status and Survival in Non-Small-Cell Lung Cancer"](#) [Journal of Clinical Oncology 8:9-15, 1990]
-  ["Results of Clinical Evaluation of Hydrazine Sulfate"](#) [VOPROSY ONKOLOGII 36:721-726, 1990]
-  ["Altered Metabolism and Mortality in Patients With Colon Cancer Receiving Chemotherapy"](#) [American Journal of the Medical Sciences 310:48-55, 1995]
-  ["Influence of Hydrazine Sulfate on Abnormal Carbohydrate Metabolism in Cancer Patients with Weight Loss"](#) [Cancer Research 44:857-861, 1984]
-  ["Treatment of Primary Brain Tumors With Sehydryn \[Hydrazine Sulfate\]"](#) [VOPROSY ONKOLOGII 40:332-336, 1994]
-  ["Hydrazine Sulfate in Cancer Patients With Weight Loss: A Placebo-Controlled Clinical Experience"](#) [Cancer 59:406-410, 1987] *
-  ["Anabolic Profiles in Late-Stage Cancer Patients Responsive to Hydrazine Sulfate"](#) [Nutrition and Cancer 3:13-19, 1981]
-  ["Effect of Hydrazine Sulfate on Whole-body Protein Breakdown Measured by ¹⁴C-Lysine Metabolism in Lung Cancer Patients"](#) [Lancet 2:241-244, 1987]
-  ["Hydrazine Sulfate: A Current Perspective"](#) [Nutrition and Cancer 9:59-66, 1987]
-  ["Experience of the treatment with Sehydryn \(Hydrazine Sulfate, HS\) in the advanced cancer patients"](#) [Investigative New Drugs 13:89-97, 1995]
-  ["Use of Hydrazine Sulfate in Terminal and Preterminal Cancer Patients: Results of Investigational New Drug \(IND\) Study in 84 Evaluable Patients"](#) [Oncology 32: 1-10, 1975] *

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TITLE:

Use of hydrazine sulfate in terminal and preterminal cancer patients: results of investigational new drug (IND) study in 84 evaluable patients.

AUTHOR:

Gold J

SOURCE:

Oncology 1975;32(1):1-10

NLM CIT. ID:

76101548

ABSTRACT:

In a series of 84 various evaluable disseminated cancer patients treated with hydrazine sulfate as a result of a pharmaceutical-sponsored investigational new drug (IND) study, it was found that 59/84 or 70% of the cases improved subjectively and 14/84 or 17% improved objectively. Subjective responses included increased appetite with either weight gain or cessation of weight loss, increase in strength and improved performance status and decrease in pain. Objective responses included measurable tumor regression, disappearance of or decrease in neoplastic-associated disorders and long-term (over 1 year) 'stabilized condition'. Of the overall 59 subjective improvements 25 (42%) had no concurrent or prior (within 3 months) anticancer therapy of any type. Of the 14 objective improvements 7 (50%) had no concurrent or prior anticancer therapy. Of the remaining cases in which there was either concurrent or prior anticancer therapy, improvements occurred only after the addition of hydrazine sulfate to the treatment regimen. Duration of improvement was variable, from temporary to long-term and continuing. Side effects were mild, comprising for the most part low incidences of extremity paresthesias, nausea, pruritis and drowsiness; there was no indication of bone marrow depression.

MAIN MESH

Hydrazines/ADVERSE

SUBJECTS:

EFFECTS/PHARMACOLOGY/*THERAPEUTIC USE
Neoplasms/*DRUG THERAPY/METABOLISM

ADDITIONAL

Drug Evaluation

MESH

Gluconeogenesis/DRUG EFFECTS

SUBJECTS:

Human

Paresthesia/CHEMICALLY INDUCED

Remission, Spontaneous

PUBLICATION JOURNAL ARTICLE

TYPES:

LANGUAGE: Eng



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TITLE: Hydrazine sulfate in cancer patients with weight loss. A placebo-controlled clinical experience.

AUTHOR: Chlebowski RT; Bulcavage L; Grosvenor M; Tsunokai R; Block JB; Heber D; Scrooc M; Chlebowski JS; Chi J; Oktay E; et al

SOURCE: Cancer 1987 Feb 1;59(3):406-10

NLM CIT. ID: 87077829

ABSTRACT: Hydrazine sulfate was evaluated using 24-hour dietary recalls and body weight determinations before and after 30 days of either placebo or hydrazine (60 mg, 3 times/d) oral administration in 101 heavily pretreated cancer patients with weight loss. After 1 month, 83% of hydrazine and only 53% of placebo patients completing repeat evaluation maintained or increased their weight (P less than 0.05). In addition, appetite improvement was more frequent in the hydrazine group (63% versus 25%, P less than 0.05). Although caloric intake was only slightly greater in hydrazine-treated patients, an increased caloric intake was more commonly associated with weight gain in patients receiving hydrazine compared with those receiving placebo (81% versus 53%, respectively). Hydrazine toxicity was mild, with 71% of patients reporting no toxic effects. Hydrazine sulfate circulatory levels were obtained from a subset of 14 patients who completed 30 days of treatment, with a single sample obtained in the morning at least 9 hours after the last dose. Mean maintenance hydrazine sulfate levels, determined using a spectrofluorometric assay, ranged from 0 to 89 ng/ml (mean 45 +/- 16 ng/ml). These data, which demonstrate an association between 1 month of hydrazine sulfate administration and body weight maintenance in patients with cancer, suggest future clinical trials of hydrazine sulfate are indicated to definitively assess its long-term impact on important clinical outcome parameters in defined cancer populations.

MAIN MESH SUBJECTS: Cachexia/*DRUG THERAPY/ETIOLOGY
Hydrazines/*THERAPEUTIC USE
Neoplasms/*COMPLICATIONS/DRUG THERAPY

Chapter 5

HYDRAZINE SULFATE

Hydrazine sulfate, a simple, off-the-shelf chemical, dramatically reverses cachexia (ka-KEK-si-a), the wasting-away process that kills two-thirds of all cancer patients. This inexpensive drug, with little or no side effects, also has a clinically documented antitumor action. It causes malignant tumors to stop growing, to reduce in size, and, in some cases, to disappear. A growing number of cancer patients diagnosed as terminal have experienced tumor stabilization and remission through hydrazine sulfate therapy.

About half of all patients who take hydrazine sulfate experience weight gain, restored appetite, extended survival time, and a significant reduction in pain and suffering. Many patients report an increase in vigor and strength and the disappearance of symptoms of the disease, along with feelings of well-being and optimism.

While hydrazine sulfate may not be a sure-fire cancer cure, large-scale clinical trials suggest that it affects every type of tumor at every stage. It can be administered either alone or in combination with cytotoxic chemotherapy or radiation to make the cancer more vulnerable to these standard forms of treatment.

Hydrazine sulfate is now undergoing Phase III trials sponsored by the National Cancer Institute. It is available to patients as a "compassionate IND [Investigational New Drug]," a designation conferred by the Food and Drug Administration on a case-by-case basis, so it is no longer, strictly speaking, an "unconventional therapy." Yet even though hundreds of patients across the country are using the drug, it is not widely discussed or disseminated among practicing physicians and its promise remains largely untapped twenty-four years after it was first proposed as an anticancer treatment by Dr. Joseph Gold. Meanwhile, hydrazine sulfate is widely available in the Com-

monwealth of Independent States (formerly the Soviet Union), where researchers have followed up on Gold's pioneering work with over ten years of investigation supporting the drug's effectiveness.

"We've gone from a red light to a yellow light, and hopefully will go to a green light," says Dr. Gold, director of the Syracuse Cancer Research Institute in Syracuse, New York, which he founded in 1966. Since his discovery in 1968 that hydrazine sulfate can prevent the wasting-away process in cancer patients and inhibit tumor growth, Gold has waged a courageous uphill battle to win acceptance for his nontoxic chemotherapy by the medical establishment.

The American Cancer Society put hydrazine sulfate on its Unproven Methods blacklist in 1976. It condemned and stigmatized the drug following a clinical trial on twenty-nine patients at Memorial Sloan-Kettering Cancer Center in New York. But it is now widely acknowledged that the Sloan-Kettering tests were botched.

When Dr. Gold made an unannounced visit to the hospital in 1974, he discovered, to his horror, that "many patients in the study were either being underdosed or overdosed. Some people who were beginning to show anticachexia response were suddenly being given 90 to 100 milligrams at one time. All this was in clear violation of the drug protocols and of our joint agreements," said Gold.¹ The study's protocol called for patients to receive 60 milligrams once a day for the first three days, twice a day for the next three days, and three times a day for the following six weeks. Therefore, some patients were getting a 67 percent overdose.

In a letter of protest to Sloan-Kettering,² Gold pointed out that some patients were receiving a massive, single dose of approximately 120 to 190 milligrams a day (instead of the usual two or three 60-milligram doses), "which quickly wiped out whatever good response they were beginning to show." The study was so poorly executed that it could never be published today, he maintains.

Nevertheless, the damage was done. The ACS's blacklisting of hydrazine sulfate caused Gold's funding to dry up and scared away other researchers from following up on his early papers.

But Gold refused to give up. In 1975, he did a study of the drug's effects on eighty-four advanced cancer patients. A total of 70 percent of them experienced weight gain (or the cessation of weight loss) and reduced pain. Only 17 percent showed tumor improvements. Meanwhile, Russian scientists at Leningrad's Petrov Research Institute were getting impressive results. In one study of forty-eight terminal cancer patients treated with hydrazine sulfate, 35 percent had tumor

stabilization or regression and 59 percent showed "subjective response" (ability to function normally, complete disappearance or marked reduction of pain, and so forth).

As a result of these and other favorable studies, the American Cancer Society announced in 1979 that it was removing hydrazine sulfate from its official blacklist. Only four other "unproven methods" that were once stigmatized on the ACS list as "quackery" had been removed from it. However, the ACS included hydrazine sulfate in the 1979 edition of the Unproven Methods list, and that edition continued to be circulated until 1982. Hydrazine sulfate was finally removed from the list the next time the list was revised, in July 1983.

Tim Hansen, now in his early twenties, of Minneapolis, Kansas, is a person grateful for the existence of hydrazine sulfate therapy. In August 1984, when he was eleven years old, Tim was diagnosed with three inoperable malignant tumors that were growing quickly in his brain. He was placed on radiation therapy, but his health steadily deteriorated until, by early 1985, his weight had dropped to fifty-five pounds. "The radiation harmed his mental functioning, and in January 1985 the surgeon told me that Tim had one week to live," says Gloria Hansen, Tim's mother.

In February, after reading a short item about hydrazine sulfate in *McCall's*, Gloria and her husband, Ray, got in touch with Dr. Gold and Tim was put on hydrazine sulfate therapy by his physicians in Kansas. By August, his weight was up to seventy-five pounds. By early 1987, two of Tim's tumors had completely vanished. In January 1988, a computerized axial tomograph (CAT scan) revealed further shrinkage of the remaining tumor, located in the base of the brain. Dr. Gold plans to keep Tim on the hydrazine sulfate protocol until the tumor is completely gone. Tim graduated from high school in 1990 and now studying electronics at a trade school, getting A's and B's.

Dr. Gold first stumbled upon hydrazine sulfate's anticancer properties during his methodical quest for a specific type of therapy. Cancer has two principal devastating effects on the body. One is the invasion of the tumor into the vital organs, with the destruction of the organs' functions—the most common cause of cancer death in the public's mind. In reality, however, this accounts for only about 10 percent of the country's half-million annual cancer deaths.

The other devastating effect of cancer is cachexia, the terrible wasting away of the body, with its attendant weight loss and debilitation. In cancer, as in AIDS, patients succumb to the accompanying illness which they would otherwise survive if not for the wasting syndrome

"In a sense, nobody ever dies of cancer," notes Dr. Harold Dvorak, chief of pathology at Beth Israel Hospital in Boston. "They die of something else—pneumonia, failure of one or another organs. Cachexia accelerates that process of infection and the building-up of metabolic poisons. It causes death a lot faster than the tumor would, were it not for the cachexia."⁴

Halting the wasting syndrome instead of directly attacking the cancer cells with poison was Dr. Gold's plan of attack. As he explains, "Each of these processes [the tumor invasion of vital organs and cachexia] has its own metabolic machinery, each is amenable to its own therapy, and each is to some degree functionally interdependent on the other. In the interest of treating the totality of malignant disease, each of these processes warrants intervention. Such an approach, dealing with *both* major underpinnings of the cancerous process—mitogenic and metabolic—affords the greatest promise for eliciting long-term, symptom-free survival and the potential for disease eradication."⁵

But what causes cachexia? Cancer cells gobble up sugar ten to fifteen times more than normal cells do. The sugar consumed by the cancer cells is generated mainly from the liver, which converts lactic acid into glucose. (Normal cells are far more efficient users of glucose, which they derive from the food we eat, not from lactic acid.) When cancer cells use sugar (glucose) as fuel, they only partially metabolize it. Lactic acid—the waste product of this incomplete combustion—spills into the blood and is taken up by the liver. The liver then recycles the lactic acid (and other breakdown products) back into glucose, and the sugar is consumed in ever-increasing amounts by voracious cancer cells. The result is a vicious cycle, what Dr. Gold calls a "sick relationship" between the liver and the cancer. The patient's healthy cells starve while the cancer cells grow vigorously. Some healthy cells even *dissolve* to feed the growing tumor.

To break this sick relationship, Gold reasoned, all he needed was to find a safe, nontoxic drug that inhibits *gluconeogenesis* (the liver's recycling of lactic acid back into glucose). In 1968, he outlined his theory in an article published in *Oncology*. "The silence was deafening," he recalls.

A year later, by a remarkable coincidence, Gold heard biochemist Paul Ray deliver a paper explaining that hydrazine sulfate could shut down the enzyme necessary for the production of glucose from lactic acid. Gold had chanced upon an eminently logical way of starving cancer. He immediately tested hydrazine sulfate on mice and found that in accordance with his theory, the drug inhibited both gluconeogenesis and tumor growth.

Over the years, many dramatic remissions in patients on hydrazine sulfate therapy have been reported. In one case, a sixty-two-year-old woman with widely disseminated cancer of the cervix, in a very debilitated condition, was put on the drug. After one week, a secondary tumor the size of an orange had completely disappeared, much to the amazement of the woman's doctors, and neck nodes had become markedly smaller. After three weeks on the therapy, the patient had gained weight and was active and in good spirits. The woman was discharged from the hospital a short time later.⁶

In 1987, Erna Kamen, a sixty-three-year-old lung cancer patient, was administered hydrazine sulfate after her discharge from a Sarasota, Florida, hospital. "Basically, my mother was sent home to die," says Jeff Kamen, an Emmy-winning television reporter. "She'd lost a significant amount of weight by then, and she had no appetite and virtually no will to do anything."

A doctor had told Jeff's father, Ira Kamen, that hydrazine sulfate offered at least "a shot in the dark." So one Monday in August 1987 a home nurse gave Mrs. Kamen one hydrazine sulfate pill shortly before serving lunch. "On Tuesday morning," recalls Jeff, "there was a commotion in the house. My mother had risen from her bed like the phoenix rising from the ashes. She was demanding that the nurse bring her downstairs so that she could have breakfast with me. . . . When people you love get into this kind of facedown with death you're just incredibly grateful for each moment."⁷

As Jeff describes his mother's recovery, "her searing pain was gone her appetite returned at a gallop." Within three weeks, her racking cough had vanished and she could walk unaided. "In the months before her death, she went on television with me to tell the nation about hydrazine sulfate. The National Cancer Institute stopped trashing hydrazine sulfate and began referring inquiries to the UCLA Medical School team whose work had validated the effectiveness of the drug long before Erna Kamen began taking it."⁸ Jeff attributes his mother's death months later to her being "mistakenly taken off hydrazine sulfate and subjected to an unproven experimental substance."

With cancer patients, hydrazine sulfate is usually administered orally in 60-milligram capsules or tablets, approximately one to two hours before meals. It is given at first once a day for several days, then twice a day, then three or four times daily, depending on the patient's response and the physician's judgment. On such a regimen, many terminal and semiterminal patients have derived considerable benefit, although patients in the early stages of the disease derive the most benefit from the treatment.

Approximately half of the patients to whom the drug is properly administered in the early stages of the disease show an almost immediate weight gain and reversal of symptoms; in some instances, the tumor eventually disappears. The common types of cancer most frequently reported to benefit from hydrazine sulfate therapy are recto-colon cancer, ovarian cancer, prostatic cancer, lung (bronchogenic) cancer, Hodgkin's disease and other lymphomas, thyroid cancer, melanoma, and breast cancer. Some less common types of cancer also benefit.

"Whether hydrazine sulfate should be used in conjunction with other agents seems to be dependent on whether these agents are doing the patient any demonstrable good," according to Dr. Gold. "In the instances in which these agents have been doing good, hydrazine sulfate should be used in conjunction with them. However—and especially with those cases on toxic drugs—in instances in which the drugs have been doing no evident good, it is probably best to withdraw such drugs and use hydrazine sulfate alone." Many alternative therapists disagree. They see hydrazine sulfate as mainly an adjunctive treatment, albeit a potentially powerful one.

Critics have made much of the fact that hydrazine sulfate, a common industrial chemical, is found in such products as rocket fuel, insecticides, and rust-prevention agents. For medical purposes, however, the salt is refined, purified, and used in reagent-equivalent grades. Given to patients in minuscule amounts, it occasionally produces mild, transient side effects such as nausea, dizziness, itching of the skin, drowsiness, and euphoria, but such side effects are minimal, especially when compared with the devastating effects of standard chemotherapy.

A very small percentage of patients undergoing long-term, high-dosage hydrazine sulfate therapy experience pain or temporary numbness in their extremities, but this condition is quickly controlled by reducing the dosage and administering vitamin B₆. In no known cases has hydrazine sulfate depressed or destroyed white blood cells or bone marrow, as conventional chemotherapy often does. In general, toxicity has been exceedingly low or nil.

The most recent study of this drug, however, concluded that hydrazine sulfate appears not to be beneficial and may even have neurological side effects. This study involved a nationwide, twenty-month trial with 291 advanced non-small-cell lung cancer patients, all of whom received chemotherapy. In the double-blind phase, half were given hydrazine sulfate, while the other half received a placebo. Patients receiving hydrazine sulfate had a median survival of 7.62 months, while the

comparable figure for those on placebo was 7.5 months. Hydrazine sulfate had no effect on cancer cachexia, according to Michael Kosty, M.D., an oncologist with Scripps Clinic and Research Foundation in La Jolla, California, who was the study's principal investigator, nor were differences noted between the two groups in anorexia or weight gain. Furthermore, the placebo group rated their quality of life higher than did those patients taking hydrazine sulfate, and some hydrazine sulfate patients experienced loss of sensation and motor function. "Therefore, the best we can say about this drug is that it has no effect and may even be deleterious," Dr. Kosty was quoted as saying in a summer 1992 issue of *ASCO Highlights*, a publication of the American Society of Clinical Oncology.

Dr. Rowan Chlebowski, director of a UCLA research project on hydrazine sulfate, conservatively estimates that the drug could benefit about half a million cancer patients each year in the United States alone.⁹ His team has conducted many clinical studies of hydrazine over two decades. Dr. Chlebowski says that the drug's indirect mode of action against tumors is problematic to more cautious investigators. "We found that hydrazine sulfate was an anticachexia agent that indirectly induced antitumor responses without much toxicity. Its action is not directed at cancer cells yet it may profoundly affect them."¹⁰

Dr. Chlebowski and his colleagues at the Harbor-UCLA Medical Center in Torrance, California, recently found evidence that hydrazine sulfate added to conventional chemotherapy improves the nutritional status and prolongs the life of patients with non-small-cell lung cancer, especially deadly forms of the disease. In the January 1990 issue of the prestigious *Journal of Clinical Oncology*, he reports that earlier-stage patients have a median survival time of at least 328 days, compared to 209 days for the placebo group. There is no curative therapy for this type of lung cancer, so the results, if confirmed, seem promising.

The wasting syndrome seen in cancer patients is also a prime risk factor for AIDS patients with Kaposi's sarcoma. There is evidence that hydrazine sulfate's capacity to stop cachexia may save many AIDS patients. Currently, Dr. Chlebowski is planning a study to test hydrazine sulfate as an anticachexia agent in patients who are infected with HIV and have lost weight.

Even though hydrazine sulfate is now undergoing extensive Phase III trials sponsored by the National Cancer Institute, resistance to this inexpensive, nontoxic chemotherapy in orthodox medical circles persists. Dr. Vincent DeVita, former director of the NCI, told a

Washington Post reporter in 1988 that he thought hydrazine was a no-hum idea." Dr. Gold, until recently, has been frozen out of the war on cancer." Two articles on cachexia published in July 1990 in the prestigious *Cancer Research* journal fail to reference any of Gold's path-breaking work, and one even denies there is any effective treatment for the wasting-away syndrome.

Dr. Gold, who does not treat patients, says that the cost of hydrazine, at most, should be nominal—comparable to the daily cost of insulin and other supplies for diabetics. "Until a pharmaceutical company sponsors the drug through the FDA, it will not be widely in use," he predicts, adding, "However, with the new studies, drug companies will suddenly begin to take notice of this most exemplary drug."

Resources

Syracuse Cancer Research Institute
Presidential Plaza
600 East Genesee Street
Syracuse, NY 13202
Phone: 315-472-6616

For further information on hydrazine sulfate and details on treatment.

Reading Material

The Cancer Industry: Unravelling the Politics, by Ralph W. Moss (see appendix A for description).

Part Two

IMMUNE THERAPIES

The immune system is your body's major line of defense in the battle against cancer and infection. Specialized cells in your immune system can recognize cancer cells as foreign and destroy them. The aim of immune therapies is to bolster those parts of the immune system that combat and eliminate cancer cells. Most other alternative therapies, though not strictly immunotherapies, also stimulate the body's natural defenses.

Several forms of orthodox immunotherapy are currently being explored in clinics and cancer centers. They are still used almost totally as adjuncts to chemotherapy, radiation, and surgery. While these orthodox immune therapies are said to hold great promise, they remain largely experimental. In contrast, the three alternative immune therapies discussed in Part Two of *Options* are used by many patients as full-fledged programs, though these treatments have been condemned, persecuted, or shunned by the medical establishment without an in-depth investigation into their possible merit. Most conventional physicians, trained to be aggressive in their approach to fighting disease, are cool toward the idea of strengthening the body's gentle self-healing powers and its natural resistance to cancer.

Cancer cells are believed to form every day in the healthy person, but a strong immune system can easily detect and destroy them before they have an opportunity to divide and proliferate. Unfortunately, for various reasons—poor nutrition, the massive pollution in our environment, stress, aging—the immune system sometimes fails to recognize the cancer cells as an enemy, and the cancer begins its slow, insidious growth over a number of years while you continue to be unaware of it.

Your immune system is normally on constant alert, scanning your body for "foreigners" such as bacteria, viruses, and abnormal cells. As soon as a foreign body is recognized, your whole system springs into action. Highly mobile *natural killer cells*, specialized to destroy foreign-

ers, are your body's first line of defense. If the cancer cells evade the natural killer cells, they proliferate and manufacture *antigens*, which are telltale substances detected by the *T-cells*, your immune system's second line of defense against tumor growth. Specialized T-cells (or *T-lymphocytes*) destroy cancerous and virus-infected cells. (The "T" in *T-cell* stands for "thymus-derived" because these white blood cells, created in the bone marrow, are carried to the thymus gland, which transforms them into T-cells.) Other white blood cells, *macrophages* (Greek for "big eaters"), ingest the cancer cells. A wide range of other cells and substances that make up the immune system help to orchestrate a coordinated attack against almost any invader.

Altogether, there are five major types of orthodox immunotherapy. The first is *BCG*, a tuberculin vaccine used in the treatment of cancer that stimulates macrophages to kill cancer cells. Consisting of a weakened strain of the tuberculosis bacillus, *BCG* (which stands for *bacillus Calmette-Guérin*) apparently works best when combined with chemotherapy; yet as a solo treatment, it has brought about some complete remissions and many cases of temporary or prolonged remission. Used by conventional as well as alternative doctors, BCG has been particularly successful in treating malignant melanoma. It appears to work well when injected directly into tumors visible on the skin, though it has also been used to treat lung cancer and other forms of the disease. One of the researchers who discovered BCG's anticancer potential was Dr. Lloyd Old, who later became director of the Sloan-Kettering Institute for Cancer Research.

Interferon is a family of proteins produced by the white blood cells in response to viral infection. It stimulates the production of macrophages and *lymphocytes* (white cells), blocks the growth of tumor cells, and transforms some lymphocytes into natural killer cells. Hyped as a wonder therapy and miracle cure when it was first synthesized in 1980, synthetic interferon turned out to be very expensive and have toxic side effects. It produces fever, chills, and muscle contractions so severe that they may require morphine.¹ Today, interferon is approved for use in the treatment of two rare forms of cancer, hairy-cell leukemia and juvenile laryngeal papillomatosis. It may have limited value in a number of other rare conditions. The FDA approved its use for AIDS patients in 1988, but it has largely been a failure in ARC-AIDS trials. Infected people who received it had flu-like symptoms, fatigue, swelling, headaches, and even hallucinations.

Interleukin-2, a protein produced by the T-cells, was also hyped by the cancer industry and the major news media as a cancer breakthrough. The results to date, however, have been disappointing. IL-2, as it is called, has reportedly been effective in some patients with melanoma

and renal cancer, but its drawbacks are major and became evident early on. Charles Moertel, M.D., of the Mayo Clinic, charged that IL-2 is highly toxic, hugely expensive, and not particularly effective.² Its side effects include fever, chills, malaise, swelling of the spleen, anemia requiring multiple transfusions, severe bleeding, shock, and confusion. Treatment with IL-2, according to Dr. Moertel, may require weeks of hospitalization in an intensive care unit "to survive the devastating toxic reactions." After a few patients died because of interleukin-2, the National Cancer Institute, which had eagerly presented it to the public as a miracle drug, withdrew such claims.⁴

Tumor necrosis factor (TNF), produced in the body in minute quantities, seems to kill cancer cells by destroying their cell membranes, although whether this happens is not clear. Side effects occur regularly; most patients develop fever and chills as well as some nausea and vomiting.⁵ Injected in cancerous mice, TNF causes their tumors to melt away. It is currently being tested to determine its potential efficacy in treating human cancer patients. Some observers believe that TNF, upon which the cancer establishment has spent millions, is simply *tumor antibody*, one of the four blood fractions used by Lawrence Burton, pioneer of a nontoxic immune therapy used in the diagnosis and treatment of cancer (see Chapter 6).

Monoclonal antibodies are synthetic antibodies created through genetic splicing, fusing a cancer patient's white blood cells with his or her cancer cells. When these bizarre *hybridomas* are reintroduced into the patient's body, they manufacture specific antibodies said to attack only the cancer cells. Attached to anticancer drugs or natural toxins, monoclonals serve as "guided missiles" by directing the antibodies they manufacture toward their malignant prey. Still in the investigative stage, monoclonals—like interferon, interleukin-2, and TNF—promise to be tremendously expensive, a boon to the pharmaceutical-medical monopoly if they are ever used in cancer treatment. They are frequently touted by the media as the next cancer breakthrough.

The American Cancer Society freely admits that it will take "many years to find the proper role of these [orthodox immunotherapy] agents in cancer treatment."⁶ Observers say this means twenty years or more. Meanwhile, the ACS continues to use its enormous power and influence to restrict or suppress safe, nontoxic cancer therapies that have produced remarkable clinical results in human beings, such as the immunotherapies of Lawrence Burton, Ph.D. (Chapter 6) and Virginia Livingston, M.D. (Chapter 7), or the biologically based therapy of Stanislaw Burzyński, M.D. (Chapter 2).

Ironically, *Coley's mixed bacterial vaccine*, which has perhaps shown

a greater cure rate than any other cancer treatment, is totally unavailable. Dr. William Coley (1862–1936), an eminent New York City surgeon and Sloan-Kettering researcher, in the 1890s developed a vaccine made of bacterial toxins that activated immune-resistance mechanisms in cancer patients and cured hundreds. His daughter, Helen Coley Nauts, D.Sc., has preserved and carried forward his important work. Yet, despite the successful use of bacterial vaccines amply reported in the medical literature since the turn of the century, today's big drug companies have no interest in what they view as merely an unprofitable item.

Staphage Lysate, a nonspecific bacterial vaccine made from *staphylococci*, is legally sold today as a specific therapy for acute and chronic staphylococcal infections. Unofficially, it has been widely used by pragmatic doctors who have had encouraging results in treating multiple sclerosis, cancer, herpes, allergies, arthritis, asthma, and many other conditions.⁷ Relatively inexpensive and almost totally nontoxic, Staphage Lysate can be inhaled, injected, or taken orally. It is known to increase the production of T-lymphocytes and to induce the natural formation of interferon and *interleukin-1*, the predecessor of interleukin-2.

Immune therapies, whether orthodox or alternative, are generally used as a treatment of last resort after patients have received toxic chemotherapy or radiation. Many doctors believe that the prior use of immune-destroying, often carcinogenic conventional treatments lowers a patient's chances for recovery through immune therapy. Chemotherapy often accomplishes the destruction of the immune system, and radiation can cause severe, prolonged immune deficiency. At any one time, there are thousands of cancer patients in the United States undergoing aggressive chemotherapy who would benefit from any immune-enhancing measures whatsoever, even supportive nutrition or vitamin supplementation.

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Hydrazine Sulfate in Cancer Patients With Weight Loss A Placebo-Controlled Clinical Experience

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Hydrazine sulfate was evaluated using 24-hour dietary recalls and body weight determinations before and after 30 days of either placebo or hydrazine (60 mg, 3 times/d) oral administration in 101 heavily pretreated cancer patients with weight loss. After 1 month, 83% of hydrazine and only 53% of placebo patients completing repeat evaluation maintained or increased their weight ($P < 0.05$). In addition, appetite improvement was more frequent in the hydrazine group (63% versus 25%, $P < 0.05$). Although caloric intake was only slightly greater in hydrazine-treated patients, an increased caloric intake was more commonly associated with weight gain in patients receiving hydrazine compared with those receiving placebo (81% versus 53%, respectively). Hydrazine toxicity was mild, with 71% of patients reporting no toxic effects. Hydrazine sulfate circulatory levels were obtained from a subset of 14 patients who completed 30 days of treatment, with a single sample obtained in the morning at least 9 hours after the last dose. Mean maintenance hydrazine sulfate levels, determined using a spectrofluorometric assay, ranged from 0 to 89 ng/ml (mean 45 ± 16 ng/ml). These data, which demonstrate an association between 1 month of hydrazine sulfate administration and body weight maintenance in patients with cancer, suggest future clinical trials of hydrazine sulfate are indicated to definitively assess its long-term impact on important clinical outcome parameters in defined cancer populations.

Cancer 59:406-410, 1987.

WEIGHT LOSS commonly accompanies cancer development and is associated with an adverse prognosis.¹⁻³ Although intensive caloric support now can be provided such patients, clinical trials evaluating caloric provision alone have not reported improved outcome for chemotherapy-treated populations with advanced cancer.⁴⁻⁶ As a result, consideration of potential mechanisms underlying the development of weight loss in the cancer population has led to development of alternative strategies for clinical intervention in these patients. Altered glucose metabolism is a common metabolic abnormality in cancer patients with weight loss,⁷⁻¹³ and it has been suggested that the inappropriate activation of pathways of glucose metabolism leads to futile cycling and cachexia devel-

opment in this population.¹⁴ If this hypothesis is correct, amelioration of the abnormal carbohydrate metabolism could provide a therapeutic approach to the adverse outcome associated with cachexia development in the cancer-bearing host.

We previously demonstrated that hydrazine sulfate is metabolically active, improving the abnormal glucose tolerance and reducing the increased glucose production rates seen in cancer patients with weight loss.¹³ We now report clinical observations on short-term hydrazine sulfate use in a cancer population with weight loss using a prospective placebo-controlled study design.

Materials and Methods

The criteria for inclusion in this trial were: a diagnosis of advanced cancer; weight loss greater than 10% from usual body weight; absence of severe hepatic or renal dysfunction (bilirubin greater than 3 mg/dl and/or creatinine greater than 2 mg/dl); and normal mental status. Patients with a known history of diabetes mellitus or those receiving corticosteroid therapy were ineligible. Patients with ascites or clinically significant edema were not entered to avoid confounding weight determinations. Patients were entered either prior to receiving systemic chemotherapy or when a new systemic therapy program was initiated

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Supported in part by Grant CA37320 from the National Cancer Institute, NIH; Grant RD-163 from the American Cancer Society; and Grant RR-00425 (General Clinical Research Center) from the NIH.

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Accepted for publication September 9, 1986.

for disease progression. Measurable disease parameters were not required, and concurrent chemotherapy was permitted. Both initial and repeat assessment of all study parameters, however, were conducted at least 2 days before and 4 weeks after chemotherapy administration.

After informed consent was obtained, patients underwent an initial assessment of nutritional parameters, including caloric intake as described below. Patients subsequently were treated with capsules containing hydrazine sulfate (60 mg) or placebo which were prepared by Anabolic, Inc. (Irvine, California). Hydrazine sulfate was given under IND 17, 671 from the Food and Drug Administration (FDA) (obtained by Dr. Chlebowski). All institutional requirements for human subjects review were met. The treatment program consisted of an escalating schedule of capsules containing either hydrazine sulfate or placebo until the full dosage of 60 mg, 3 times/d given before meals, was reached beginning on the 8th day. This program was based on the extensive Russian experience.¹⁵ Patients were contacted weekly to assess compliance and kept daily compliance diaries. The validity of daily compliance diaries was checked against intake based on returned prescription bottles. Following 30 days of either agent, the assessment of body weight, caloric intake, and other parameters was repeated.

During the initial and repeat evaluation, all patients received determination of body weight measured on the same printing scale; anthropometrics, including tricep skinfold thickness, mid-arm muscle circumference, and serum albumin; caloric intake using a 24-hour dietary recall history obtained by nutritionists and computer analyzed to give protein, carbohydrate, fat, and energy contents of the diet. Expected caloric intake was normalized for each patient by weight based on a calculated recommended daily allowance (RDA). Toxic effects of treatment and influence on appetite were determined by questionnaire.

In a subset of 14 patients, blood samples for hydrazine sulfate circulatory levels were obtained as a morning sample taken at least 9 hours from the last oral dose following 30 days of treatment. Hydrazine sulfate levels were measured using a defined^{16,17} spectrofluorometric assay in which reaction of hydrazine sulfate with dimethylaminobenzaldehyde produces a colored derivative. Fluorescence was subsequently determined in an Aminco Bowman (Silver Spring, MD) spectrophotofluorometer with an excitation wavelength of 466 nm and emission wavelength of 546 nm.

All patients were given defined, uniform dietary counselling based on nutritional status at entry to insure comparability of dietary information available to patients on hydrazine or placebo treatment. The nutritional guidelines all patients were provided with were designed to duplicate a routine clinical dietary assessment that would be expected to be a component of a cancer patient's standard

TABLE 1. Pretreatment Characteristics of Cancer Patients Receiving Hydrazine Sulfate or Placebo

	Treatment received	
	Hydrazine	Placebo
Number entered	71	30
Age in years		
Median	56	59
Range	32-77	36-77
Sex (% Male)	61%	65%
Disease type		
Lung	46	15
Colon	13	4
Other breast	4	3
Esophagus	2	3
Nasopharyngeal	3	1
Hepatocellular	1	2
Ovarian	2	1
Prostate	0	1
Performance score		
(0 or 1)	14%	23%
(2 or 3)	86%	77%
Nutritional status		
% Weight loss (mean)	17%	14%
Caloric intake		
≥90% of RDA	39%	41%
<90% of RDA	61%	59%
Albumin gm/dl (Mean)	3.4	3.3
Concurrent chemotherapy	78%	74%

RDA: recommended daily allowance.

clinical management. Enteral tube feedings or parenteral nutritional support was not given any patient while on study.

A total of 101 patients with advanced cancer underwent initial evaluation. Sixty-one consecutive patients (including all 30 patients given placebo and 31 given hydrazine) were randomly assigned treatment in a double-blind fashion with treatment assignment based on published random-number tables. An additional 40 patients received hydrazine sulfate and represented a consecutive series of patients seen in the Clinical Research Center meeting entry criteria for the trial. Statistically significant differences between hydrazine and placebo groups relative to pretreatment clinical factors were sought using chi square contingency table analyses and Student's *t* test. The statistical differences between hydrazine and placebo treatment were determined using the two-group *t* test.

Results

A total of 101 patients with a variety of advanced cancers underwent initial evaluation. Patients receiving hydrazine sulfate or placebo were comparable with respect to tumor type, age, sex, performance score, nutritional parameters and chemotherapy experience (Tables 1 and 2). The compromised nutritional status of the study pop-

TABLE 2. Concurrent Chemotherapy of Cancer Patients Receiving Hydrazine Sulfate or Placebo According to Disease Type

Chemotherapy given	Study arm	
	Hydrazine	Placebo
Lung cancer (n)	46	15
PACcO	15	4
PVB	12	7
ACcO	9	2
ACO	2	0
No chemotherapy	8	2
Colon cancer (n)	13	4
5-FU	2	1
5-FU + vitamin K	7	1
No chemotherapy	4	2
Other disease sites (n)*	12	11
No chemotherapy	4	3

P: cisplatin (Platinol); A: doxorubicin, (Adriamycin); C: cyclophosphamide; c: CCNU; O: vincristine (Oncovin); 5-FU: 5-fluorouracil; V: vinblastine; B: bleomycin; 5-FU + vit K: 5-fluorouracil plus vitamin K₁ (Synkavite).

* The patients with other disease sites received a variety of regimens which included cisplatin in 62% and 50% of instances for the hydrazine and placebo group, respectively.

ulation is demonstrated by the 16% average weight loss experienced by the overall population. Of this advanced disease population with weight loss, 58 patients were able to complete repeat evaluations after 30 days of treatment (41 were given hydrazine; 17, placebo). Early disease progression and/or death accounted for almost all cases not having repeat study. Only two patients refused repeat evaluation.

The influence of 30 days of hydrazine sulfate or placebo therapy on study parameters for all entered patients who underwent repeat evaluation is outlined in Table 3. Weight was maintained or increased in a higher proportion of patients receiving hydrazine sulfate compared to placebo therapy (83% versus 53%, respectively; $P < 0.05$). The use of weight loss as a study parameter was not compromised by the development of ascites or significant edema, as this did not occur in any patient over the 30 day period of

TABLE 3. Influence of 30 Days of Hydrazine Sulfate or Placebo on Nutritional Status of Cancer Patients With Weight Loss

	Hydrazine n = 41*	Placebo n = 17
Weight maintained or increased (>2.5 kg)	83%†	53%
Improvement in appetite	63%†	25%
Caloric intake increased (>10% over baseline)	51%	37%
Increased caloric intake associated with weight gain (>2.5 kg)	81%†	53%

* Number completing initial and repeat study.

† $P < 0.05$ hydrazine compared to placebo group.

observation. Anthropometrics were unchanged over the 30-day study period. Caloric intake was only slightly higher in the hydrazine treated population. When all patients experiencing an increase in caloric intake were considered, however, weight gain was seen in a significantly higher proportion of patients receiving hydrazine sulfate while increasing caloric intake compared with those who increased caloric intake while receiving placebo. The results using hydrazine sulfate were closely comparable in the 31 patients entered as part of the randomized trial when compared with the 40 patients added as a consecutive series. The results for the patients receiving hydrazine or placebo who were entered as part of the randomized trial were: weight maintained or increased, 71% versus 53%; improvement in appetite, 63% versus 25%; caloric intake increased, 69% versus 37%; and increased caloric intake associated with weight gain, 77% versus 53% for the hydrazine versus placebo patients respectively. In addition, results in groups receiving or not receiving concurrent chemotherapy reflected those obtained in the entire group.

Thirty-five patients with cancer other than small cell lung cancer (the predominant tumor type studied) completed serial evaluation, with 26 receiving hydrazine sulfate and nine receiving a placebo. In the lung cancer patients, weight maintenance or increase was achieved in 83% of those receiving hydrazine sulfate compared with 33% of those receiving the placebo.

The short term hydrazine sulfate regimen used in this trial was well tolerated by study participants. Compliance forms were returned by 90% of patients who completed repeat evaluations, and indicated that 95% of the scheduled dose was taken by the study population completing 30 days of therapy. The mean maintenance plasma hydrazine sulfate levels obtained from a subset of 14 patients ranged from 0 to 89 ng/ml with a mean value of 45 ± 16 ng/ml. Clinical toxicity of patients receiving hydrazine sulfate was limited largely to mild to moderate nausea and lightheadedness with 71% of patients reporting no toxic effects from hydrazine use (Table 4). Treatment was discontinued for toxic effects in 10% of patients receiving hydrazine; while 6% of patients receiving placebo had treatment stopped for "toxic effects." Significantly, paresthesias or hypoglycemic symptoms were not reported by any patient receiving hydrazine in this trial.

Discussion

Short-term administration of hydrazine sulfate was better than a placebo in maintaining body weight and improving appetite in patients with advanced cancer in the current clinical experience. The weight effect apparently resulted from an increase in the effectiveness of the ingested calories, since a higher proportion of patients

who increased their caloric intake on hydrazine were able to maintain or improve their body weight. The association that we have reported¹⁸ between weight maintenance and improved glucose metabolism in hydrazine-treated cancer patients suggests that interruption of abnormal metabolic pathway function may underlie the improved nutritional status seen with hydrazine sulfate in the current trial. If this hypothesis can be confirmed, hydrazine sulfate could represent one of a new class of metabolic/hormonal agents¹⁹⁻²¹ directed at influencing the abnormal metabolism seen frequently in patients with cancer.

No prior clinical experience with hydrazine sulfate in cancer patients has prospectively evaluated caloric intake or included a placebo control population. Single-arm studies involving 348 Russian and 84 American patients with cancer have emphasized subjective parameters.^{15,22} In the American experience, Gold²² reported that 70% of the treatment group demonstrated subjective improvement, including increased appetite with either weight gain or cessation of weight loss, increased strength and improved performance status, or decreased pain, as measured by need for analgesics. In the Russian experience, Gershonovich^{15,23} reported that 50% of patients receiving hydrazine sulfate as their sole therapeutic intervention achieved moderate or marked improvement in cachexia with associated favorable symptomatic effects on appetite and pain. Not all clinical studies of hydrazine sulfate have shown benefit. In three small trials of hydrazine sulfate (all entering less than 30 patients) where reduction in tumor size was used as a major therapeutic endpoint, little benefit was reported.²⁴⁻²⁶ The clinical effects of hydrazine sulfate on body weight observed in the current study in conjunction with the metabolic effects of hydrazine that we reported in 1984¹² now provides a strong rationale for further studies designed to assess the impact of hydrazine sulfate on clinical outcome in defined cancer populations.

Surprisingly, thirty-seven percent of weight-losing cancer patients given placebo in this trial increased their caloric intake by more than 10%, and 53% of the placebo group maintained or increased their body weight over the 1-month observation period. This result in the placebo population may have been related to the nutritional counseling that was given in identical fashion to patients on both treatment arms in this study. Placebo controls clearly are important in trials designed to alter and assess nutritional parameters in cancer populations.

The study protocol employed in our trial was not designed to assess the influence of hydrazine sulfate on tumor growth characteristics. The short 30-day period of treatment and entry criteria preclude assessment of hydrazine sulfate influence on this parameter. Almost all of our patients with advanced solid tumors refractory to initial therapy, however, demonstrated no change in tumor dimensions during the 1-month period of observation.

TABLE 4. Patient Tolerance of Hydrazine Sulfate or Placebo Treatment

	% of Patients Treated	
	Hydrazine	Placebo
No toxic effects	71%	84%
Nausea and vomiting		
Mild	12%	12%
Moderate	5%	0%
Light-headedness	17%	6%
Treatment discontinued for toxic effects	10%	6%

The relative lack of toxicity of short-term hydrazine sulfate administration in a 60 mg 3 times/d schedule to a large cancer population receiving other concurrent chemotherapy treatment was noteworthy. In the previous limited clinical experience,^{15,22,23} only one report has emphasized significant toxicity; Ochoa and coworkers²⁴ reported a 50% incidence of polyneuritis associated with hydrazine sulfate use in a 29-patient experience. In three trials^{15,22,25} and the present report, polyneuritis was seen in less than 1% of the more than 500-patient cumulative experience. The lack of toxicity in the current experience can be documented further by the good compliance reported by the patients in their diaries. The latter result is interesting considering the somewhat wide range of hydrazine sulfate maintenance circulatory levels observed in the pharmacokinetic component of this trial. However, these results are consistent with developing pharmacokinetic information regarding the half-time of oral hydrazine sulfate administration.¹⁷ These data suggest that future clinical trials involving hydrazine sulfate should include determination of chronic circulatory levels to assess hydrazine sulfate bioavailability and permit correlation with metabolic, nutritional and clinical endpoints.

Conclusion

This experience with hydrazine sulfate in an advanced cancer population points to a potential role for this agent in maintaining weight in patients with cancer cachexia. Whether maintenance of body weight under these conditions will be associated with improvement in important clinical outcome variables and overall survival will require future prospective, long-term, placebo-controlled evaluation in cancer populations with less advanced disease given defined systemic therapy. Such studies in the non-small cell lung cancer population are currently in progress.

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Oncology 32: 1-10 (1975)

Use of Hydrazine Sulfate in Terminal and Preterminal Cancer Patients: Results of Investigational New Drug (IND) Study in 84 Evaluable Patients

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Key Words. Hydrazine sulfate therapy in advanced cancer patients · Treatment of advanced human cancer with anti-gluconeogenic drugs · Interruption of cancer cachexia as a means of cancer chemotherapy · Interruption of gluconeogenesis as a means of cancer chemotherapy

Abstract. In a series of 84 various evaluable disseminated cancer patients treated with hydrazine sulfate as a result of a pharmaceutical-sponsored investigational new drug (IND) study, it was found that 59/84 or 70 % of the cases improved subjectively and 14/84 or 17 % improved objectively. Subjective responses included increased appetite with either weight gain or cessation of weight loss, increase in strength and improved performance status and decrease in pain. Objective responses included measurable tumor regression, disappearance of or decrease in neoplastic-associated disorders and long-term (over 1 year) 'stabilized condition'. Of the overall 59 subjective improvements 25 (42 %) had no concurrent or prior (within 3 months) anticancer therapy of any type. Of the 14 objective improvements 7 (50 %) had no concurrent or prior anticancer therapy. Of the remaining cases in which there was either concurrent or prior anticancer therapy, improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Duration of improvement was variable, from temporary to long-term and continuing. Side effects were mild, comprising for the most part low incidences of extremity paresthesias, nausea, pruritis and drowsiness; there was no indication of bone marrow depression.

Hydrazine sulfate has been used as an investigational new drug (IND) for over 1 year in the treatment of advanced cancer. Its proposed mechanism of action is as a gluconeogenic blocking agent at the phosphoenolpyruvate carboxykinase (PEP CK) reaction, attenuating host energy loss as a result of increased gluconeogenesis in cancer and therefore interrupting the *systemic cycle of tumor-energy gain-host-energy loss* (tumor growth-host cachexia) (1, 2). Early reports indicated that hydrazine sulfate, administered orally to advanced cancer patients, resulted in marked subjective and objective improvements (3), subjective improvements including increase in appetite, cessation of weight loss and/or

weight gain, improved performance status, and decrease in pain; objective improvements included measurable reduction in tumor size and reduction in or disappearance of neoplastic-associated disorders (effusions, jaundice, etc.). Duration of improvements was reported as variable and side effects, minimal. In further reports (4), in which hydrazine sulfate was used in conjunction with conventional chemotherapy in patients with disseminated neoplasia, it was unclear as to which type of therapy resulted in the reported subjective and objective improvements. The present report, undertaken as a pharmaceutical-sponsored IND study and representing a series of 84 evaluable cases of various terminal and preterminal cancer patients, indicates a high degree of anticancer activity in patients treated with hydrazine sulfate alone.

Procedures and Protocols

Physician selection. This study was the result of separate inputs of many clinicians – oncologists as well as others – whose participation was under pharmaceutical IND sponsorship. As such, this study is designated as ‘uncontrolled’.

Patient selection. Patients with any type of disseminated neoplasia, who no longer responded to chemotherapy and/or radiation, were considered eligible for hydrazine sulfate therapy. A minimum prognosis of 2 months was recommended.

Drug and protocol. The drug consisted of 100 % purity hydrazine sulfate mixed with an inert starch in capsular form (pharmaceutical IND preparation) for oral administration. Protocol of drug administration was as follows: 60 mg q.d. × 4; 60 mg b.i.d. × 4; then 60 mg t.i.d. as maintenance. In patients weighing less than 50 kg, dosages were halved (i.e., 30 mg q.d. × 4; 30 mg b.i.d. × 4; then 30 mg t.i.d.). In the event that a b.i.d. schedule produced satisfactory results, this dosage schedule was maintained at the clinician's discretion. In no event was a single dosage ever to exceed 60 mg.

Concurrent anticancer medication. The continuing use of concurrent anticancer medication was acceptable if it was no longer producing a demonstrable anticancer effect by itself.

Data presentation. A 4-sheet data page (‘Patient Report Form’) was required to be completed by the clinician during the course of treatment of each patient. These data sheets included the following information: detailed history, site of tumor and metastases, prior treatments (defined in this study as any type of anticancer therapy given within 3 months of the initiation of hydrazine sulfate therapy; prior treatment data included dates of therapy, types and quantitation), concurrent medications, performance status evaluation, objective tumor size and site evaluations, subjective observation ratings and check list, laboratory data, clinician's statement of patient evaluation prior to hydrazine sulfate therapy, clinician's statement of evaluation of results of hydrazine sulfate therapy, clinician's evaluation of side effects of hydrazine sulfate therapy, and clinician's signature.

Criteria for designation as ‘improvement’. Designation of subjective improvements was made on the basis of improvements indicated in the subjective observations rating check list and/or affirmation of improvement in the clinician's statement under ‘clinician evaluation’ section. In general a subjective improvement was based on a quantitatively measurable or estimable parameter such as strength (number of hours ambulatory, quality of ambulation, etc.), appetite (food intake), weight (scale measurement) and pain (quantitative need for analgesics). Objective improvements were designated on the basis of measurable reduction in

tumor size, long-term (1 year or more) 'stabilized condition' in a previously rapidly growing neoplasm, and disappearance of or reduction in neoplastic-associated disorders. Each case in this category was to be supported by related laboratory measurements, where possible.

Criteria for designation as 'nonevaluable'. Cases were deleted from evaluation for any of the following reasons: (a) inadequate prognosis: patient survival of less than 3 weeks; (b) inadequate drug trial: drug trial of less than 3 weeks; (c) insufficient data submitted on Patient Report Form: no evaluation possible, and (d) concurrent treatment with newly initiated cytotoxic chemotherapy: patient response nonevaluable.

Results

Of a total number of 158 cases submitted in the study, 84 were evaluable and 74 nonevaluable. Of the evaluable cases 14 (17%) were categorized as 'objective (and subjective) improvement', 45 (54%) as 'subjective improvement only', and 25 (30%) as 'no improvement'. The indicated overall improvement

Table I. Categorization of evaluable cases in Investigational New Drug study of hydrazine sulfate

Site and/or type of primary tumor	Objective and subjective improvements	Subjective improvement only	No improvement	Total cases
Brain (astro, glio)	2	0	0	2
Breast (all)	2	6	2	10
Colorectal-gastric	2	12	8	22
Gallbladder	1	0	0	1
Hodgkins, stage IV	0	0	2	2
Liver (primary)	0	0	1	1
Lung (all)	2	11	2	15
Melanoma	0	1	2	3
Neurosarcoma (neck)	0	1	0	1
Ovary (all)	1	3	1	5
Pancreas	1	4	3	8
Primary unknown	0	2	0	2
Prostate	0	1	2	3
Squamous cell (neck)	0	1	0	1
Testis	0	1	0	1
Tonsil (palatine)	1	0	0	1
Urinary bladder, ureter	0	1	2	3
Uterus (cervix)	1	1	0	2
Uterus (endometrial)	1	0	0	1
Total	14	45	25	84

Table II. Nonevaluable cases: reasons for exclusion from evaluation

Inadequate prognosis survival time, weeks			Inadequate drug trial, weeks on drug			Insufficient data	New concurrent cytotoxic chemotherapy	Total cases
0-1	1-2	2-3	0-1	1-2	2-3			
11	11	9	8	6	11			
31			25			15	3	74

rate was 59/84 cases, or 70%. Of the nonevaluable cases, 31 (42%) were included under 'inadequate prognosis', 25 (34%) under 'inadequate drug trial', 15 (20%) under 'insufficient data', and 3 (4%) under 'newly initiated cytotoxic chemotherapy'. Categorization of evaluable and nonevaluable cases is given in tables I and II, respectively.

'Improvements'

Improvements were noted in tumors from almost all of the 19 reported sites of origin. No particular site of origin or tumor type was 'most susceptible' to hydrazine sulfate therapy, although the largest number of cases came from colorectal and lung carcinoma, which reflects the general incidence of these diseases in the population. The duration of improvement was variable, being reported from very temporary (1 week) to in excess of 1 year and continuing. It was possible to obtain follow-up reports in only less than half of the improved cases.

Objective responses. Of the 14 reported objective responses, 7 (50%) showed measurable tumor regression; 2 of these were accompanied by a disappearance of or reduction in neoplastic-associated disorders (effusions, jaundice, etc.). An additional 2 (14%) of the 14 cases were classified as long-term 'stabilized condition', both of which represented preterminal lung cancers whose disease had been rapidly progressive prior to hydrazine sulfate therapy. They are currently both alive and well 17 and 18 months after initiation of hydrazine sulfate therapy, respectively; neither are on any kind of concurrent anticancer therapy. The remainder of the 5 (36%) cases were classified as objective responses on the basis of amelioration of neoplastic-associated disorders, accompanied by marked subjective improvements. (In this regard all 14 cases showed subjective improvements.) All objective responses were also accompanied by tumor-related laboratory improvements, where measured.

Subjective responses. A total of 45 cases displayed subjective improvements only; this number, added to the foregoing 14 cases, gave a combined total of 59 subjectively improved cases. 48 (81%) of these showed an increase in appetite

Table III. Response analysis in improved cases

	No concurrent or prior anti-cancer therapy	Concurrent anti-cancer (incl. cyto-toxic) therapy	Concurrent steroid therapy only	Concurrent steroid and prior cyto-toxic therapy	Concurrent steroid and prior radiation therapy	Prior cyto-toxic therapy	Prior steroid therapy	Prior radiation therapy	Total cases
Objective responses	7 (50 %)	3 (21 %)	1 (7 %)	—	1 (7 %)	—	1 (7 %)	1 (7 %)	14
Subjective responses	18 (40 %)	17 (38 %)	5 (11 %)	1 (2 %)	—	3 (7 %)	—	1 (2 %)	45

with either weight gain or a cessation of weight loss. 48 (81 %) showed an improvement in performance status as measured by an increase in strength, ambulation or both. And 21 (36 %) showed a decrease in pain as measured by a diminished need for analgesics.

Ongoing concurrent (or prior) anticancer therapy. Various of the improved cases were treated with either steroids and/or cytotoxic chemotherapy and/or radiation, prior to initiation of hydrazine sulfate therapy, as indicated in table III. In all these cases the noted improvements occurred *after* the addition of hydrazine sulfate to the therapy. In regard to the objective responses 7 (50 %) of the 14 cases were treated with hydrazine sulfate alone, without concurrent or prior anticancer therapy of any type, while 7 (50 %) of the cases did receive concurrent or prior anticancer therapy. In the subjective-only responses, 18/45 or 40 % of the cases were treated only with hydrazine sulfate, without concurrent or prior anticancer therapy, while 27 of the cases (60 %) did receive concurrent or prior anticancer therapy.

'No Improvements'

Of the 25 'no improvement' cases 2 (8 %) expired within 3–4 weeks after initiation of hydrazine sulfate therapy; 2 (8 %) had very little information in their Patient Report Form so that actual categorization became difficult; 9 (36 %) had a drug trial of only 3–4 weeks, and 14 (56 %) had concurrent anticancer therapy which consisted of cytotoxic drugs, radiation, steroids or combinations thereof. *In only 5 cases* were these foregoing considerations not a factor, i.e., the patient had an adequate prognosis and drug trial, had no concurrent or prior anticancer therapy, and had sufficient information submitted on his Patient Report Form to support a categorization of 'no improvement'.

Nonevaluable Cases

The general breakdown of categories of the 74 nonevaluable cases is given above and in table II. Of a total of 31 of these cases excluded from evaluation because of inadequate prognosis (survival time), 11 died within 1 week of initiation of hydrazine sulfate therapy, 22 died within 2 weeks, and the full 31 died within 3 weeks. Of a total of 25 additional cases excluded from evaluation for reasons of inadequate drug trial, 8 were on drug for only 1 week or less, 14 were on drug for 2 weeks or less, and the full 25 were on drug for 3 weeks or less. Thus, of the 56 cases excluded from consideration for the foregoing two reasons, 19 had a survival time or drug trial of 1 week or less, 36 had a survival time or drug trial of 2 weeks or less, and the full number - 56 - had a survival time or drug trial of 3 weeks or less.

Side Effects

Side effects were determined on the basis of evaluable cases only and were in general mild. They comprised: *extremity paresthesias* (5%); this condition was diminished or eliminated by a reduction of dosage and/or administration of pyridoxine hydrochloride (vitamin B₆) in excess of 25 mg daily; *nausea* (4%), in most cases transient; nontransient nausea was eliminated by a reduction of dosage or withdrawal of medication for a period of several days, then reinstatement of treatment at lower dosage levels; *dry skin* or *transient pruritis* (3%); *'dizziness'* (1%); *'drowsiness'* (1%); *possible thrombophlebitis* (1%) (it was not known whether this condition was drug-related). The total evaluable cases showing side effects numbered 13/84 or an overall 15%. There were no deaths attributable to hydrazine sulfate therapy, either in the evaluable or in the nonevaluable cases.

Discussion

It is important that a detailed analysis of a study of this nature include not only the obviously improved cases as a result of hydrazine sulfate administration, but also the nonimproved and nonevaluable cases. Such factors as poor patient and clinician selection as well as inadequate protocol planning, must be assessed as to their quantitative contribution to the latter two categories.

Nonimproved and Nonevaluable Cases

Lack of proper patient selection, via inadequate patient prognosis and inadequate drug trial, contributed heavily to the large number of nonevaluable and nonimproved cases. Minimum protocol-recommended prognosis was 2 months, yet as many as 31/74 or 42% of the nonevaluable cases were so designated because of a survival time of 3 weeks or less, while in the nonimproved category

2/25 or 8 % of the cases had a survival time of only 3-4 weeks. In addition, as many as 25/74 or 34 % of the nonevaluable cases were so designated because of an inadequate drug trial (3 weeks or less), while 9/25 or 36 % of the nonimproved cases had a drug trial of only 3-4 weeks. Thus, in the nonevaluable category the number of combined inadequate prognosis and inadequate drug trial cases totaled 56/74 or 76 %, while in the nonimproved category the number of combined cases of 'borderline-acceptable' survival time and drug trial (3-4 weeks) totaled 11/25 or 44 %. Such large percentages, representing inadequate prognosis and inadequate drug trial, must be attributed chiefly to improper patient selection and not to the occasional misevaluations which arise in any study.

Lack of proper clinician selection was also an apparent factor in this study, manifest chiefly in those cases in which too little information was submitted. In the nonevaluable category as many as 15/74 or 20 % of the cases were so designated because of lack of sufficient information upon which to make an evaluation. Even in the nonimproved category 2/25 or 8 % of the cases had only a minimum of information submitted. Such numbers surely reflect a lack of interest or capability on the part of the clinician. (Indeed, inadequate patient selection itself may be a function of this type of clinician inadequacy.)

Poor protocol planning, manifest by the acceptability of concurrent anticancer therapy, also had a major input in these two categories. In the nonevaluable group 3/74 or 4 % of the cases were so designated because of newly initiated concurrent cytotoxic chemotherapy, rendering impossible any attributive evaluation of patient response. In the nonimproved group as many as 14/25 or 56 % of the cases had ongoing concurrent anticancer therapy which was no longer producing demonstrable clinical benefit, but which could, by virtue of its immunosuppressive and hematosuppressive effects, adversely affect or mask the results of any new drug concurrently administered. Clearly, the protocol was weakened by inclusion of any type of concurrent anticancer therapy whatsoever.

Thus, in retrospect many of the cases which fell into the nonevaluable and nonimproved categories should properly never have entered this study. This circumstance could have been obviated by better patient and clinician selection as well as by a 'tighter' protocol. It is hoped that a careful categorization in this study has dealt adequately with these factors.

Improved Cases

Despite the above-described considerations, a large number of clearly improved cases emerged in this study. This improvement, moreover, was the result of administration of hydrazine sulfate alone in a large percentage of the cases and was not influenced by any other mode of concurrent or prior anticancer therapy. Table III indicates that 50 % of the objectively improved cases (7/14) were on hydrazine sulfate alone, with no prior or concurrent anticancer therapy;

and 40 % (18/45) of the subjective-only responses were also the result of hydrazine sulfate therapy alone. This constitutes strong *prima facie* evidence indicating hydrazine sulfate to be a clinically active anticancer agent in itself. It is important to remember that even in those cases which received concurrent or prior anticancer therapy, the noted improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Thus, whether as a sole agent or in combination with other agents, administration of hydrazine sulfate to advanced cancer patients is linked to marked anticancer responses.

Moreover, hydrazine sulfate is apparently not a 'tumor-specific' agent, as can be seen from table I. Virtually all types of cancer – especially those which ultimately promote a degree of host cachexia – are apparently susceptible to its actions. Reports, in addition to those of this study, which have reached this laboratory, indicate that the spectrum of disease beneficially affected by hydrazine sulfate extends to cancers arising from all organ systems and/or tissues in the body. The most dramatic responses reported to date have been those with primary lung neoplasms, although this observation may prove to be premature as more and earlier cases are reported.

The duration of improvement has been unpredictable, but has generally been longer in those cases responding objectively (as well as subjectively). Some of the responses have been of very short duration. But others have been quite lengthy. To date three cases in this study – two primary lung and one ovarian – are alive 17, 18 and 21 months after institution of hydrazine sulfate therapy alone, respectively; all three were previously considered terminal or preterminal. Preliminary indications suggest that the improvements brought about by hydrazine sulfate therapy – whether objective or subjective – have been accompanied by extension in survival time and that the quality of this survival time was high: patients who had obtained objective response and/or increased appetite, strength and decreased pain as a result of hydrazine sulfate therapy, were reported to have been restored to a more positive orientation toward living.

The duration of improvement may also be related to the degree of advancement of the disease. The patients in this study were in general in the very latest stages of disease, yet there were many improvements, some of which were marked. However, it is generally regarded that any modality of anticancer therapy has its best chances of success when used *early* in the course of disease. And this is probably true of hydrazine sulfate. There would seemingly be no disadvantage in instituting hydrazine sulfate therapy early in the course of disease, especially in those cases where the ultimate clinical course is virtually unaffected by any known therapeutic modality. Moreover, since the toxicity of hydrazine sulfate is apparently of a low order of magnitude, unlike many of the cytotoxic drugs whose 'side effects' can produce extreme patient discomfort and death, it would seem prudent to investigate the effect of this drug on early patients, rather than use it at the very last stages as a 'resurrective' type of therapy. If

positive responses can be obtained in terminal patients — as indicated in this study — it seems only reasonable that a greater degree of positive response could be expected in early patients, as is the case with many other anticancer modalities.

Side Effects

The side effects of hydrazine sulfate are indeed of a very minor nature as reported in this study, with the possible exception of 'torpidity' or 'drowsiness' which had less than a 1 % incidence and occurred only in very advanced bedridden case(s). The most frequent side effect, occurring usually after the 6th week of therapy, appears to be the development of mild extremity paresthesias, particularly of the fingers and toes. This condition reportedly can be diminished or eliminated by dosage reduction and/or addition of vitamin B₆ (in excess of 25 mg daily) to the regimen. Other side effects such as nausea, pruritis, etc., appear to be transient in nature and not a clinical problem, with few exceptions. In general, since hydrazine sulfate is not a cytotoxic agent, there have been none of the severe side effects of these drugs reported with its use, and this is especially true of hematopoietic-suppressive effects. Hydrazine sulfate does not depress the bone marrow. On the contrary, several of the cases of this study with advanced prostatic or breast cancer showed net *elevations* in hemoglobin, hematocrit and platelets within 2 weeks of initiation of treatment. This observation has been confirmed in many case reports not a part of this study and thus is in contrast to the cytotoxic drugs, one of the prime limitations of which are their hematosuppressive effects. Finally, hydrazine sulfate has not been demonstrated clinically to possess immunosuppressive properties, although this must await verification by further basic studies.

Concluding Remark

Hydrazine sulfate therapy is a new type of chemotherapy. Its clinical use at present represents a *beginning*. Whether a study with any new drug is positive or negative, it must always be evaluated in terms of the 'state of the art'. Hydrazine sulfate represents the *first* of a class of new agents designed to interrupt host participation in cancer. Other agents in this class now in development may prove to be far superior to hydrazine sulfate. In addition, adjunctive agents to hydrazine sulfate therapy may also prove to be very important. In this respect it has already been learned by this laboratory that administration of a substance interfering with triglyceride synthesis, can greatly potentiate the anticancer action of hydrazine sulfate (paper in preparation). For these types of reasons it must be emphasized that the clinical potential of hydrazine sulfate-like drugs in cancer has only just begun to be explored, and much further work lies ahead before a more comprehensive understanding of their ultimate anticancer potential becomes clear.

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Oncology 32: 11-20 (1975)

Primary C-Cell Hyper

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Key Words. Thyroid C cells · carcinoma

Abstract. The electron mic
C-cell hyperplasia in 'hot' thyroid
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Introduction

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Joseph Gold, Syracuse Cancer Research Institute Inc., Presidential Plaza, 600 East Genesee Street, Syracuse, NY 13202 (USA)

Hydrazine Sulfate in Cancer Patients With Weight Loss

A Placebo-Controlled Clinical Experience

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Hydrazine sulfate was evaluated using 24-hour dietary recalls and body weight determinations before and after 30 days of either placebo or hydrazine (60 mg, 3 times/d) oral administration in 101 heavily pretreated cancer patients with weight loss. After 1 month, 83% of hydrazine and only 53% of placebo patients completing repeat evaluation maintained or increased their weight ($P < 0.05$). In addition, appetite improvement was more frequent in the hydrazine group (63% versus 25%, $P < 0.05$). Although caloric intake was only slightly greater in hydrazine-treated patients, an increased caloric intake was more commonly associated with weight gain in patients receiving hydrazine compared with those receiving placebo (81% versus 53%, respectively). Hydrazine toxicity was mild, with 71% of patients reporting no toxic effects. Hydrazine sulfate circulatory levels were obtained from a subset of 14 patients who completed 30 days of treatment, with a single sample obtained in the morning at least 9 hours after the last dose. Mean maintenance hydrazine sulfate levels, determined using a spectrofluorometric assay, ranged from 0 to 89 ng/ml (mean 45 ± 16 ng/ml). These data, which demonstrate an association between 1 month of hydrazine sulfate administration and body weight maintenance in patients with cancer, suggest future clinical trials of hydrazine sulfate are indicated to definitively assess its long-term impact on important clinical outcome parameters in defined cancer populations.

Cancer 59:406-410, 1987.

WEIGHT LOSS commonly accompanies cancer development and is associated with an adverse prognosis.¹⁻³ Although intensive caloric support now can be provided such patients, clinical trials evaluating caloric provision alone have not reported improved outcome for chemotherapy-treated populations with advanced cancer.⁴⁻⁶ As a result, consideration of potential mechanisms underlying the development of weight loss in the cancer population has led to development of alternative strategies for clinical intervention in these patients. Altered glucose metabolism is a common metabolic abnormality in cancer patients with weight loss,⁷⁻¹³ and it has been suggested that the inappropriate activation of pathways of glucose metabolism leads to futile cycling and cachexia devel-

opment in this population.¹⁴ If this hypothesis is correct, amelioration of the abnormal carbohydrate metabolism could provide a therapeutic approach to the adverse outcome associated with cachexia development in the cancer-bearing host.

We previously demonstrated that hydrazine sulfate is metabolically active, improving the abnormal glucose tolerance and reducing the increased glucose production rates seen in cancer patients with weight loss.¹³ We now report clinical observations on short-term hydrazine sulfate use in a cancer population with weight loss using a prospective placebo-controlled study design.

Materials and Methods

The criteria for inclusion in this trial were: a diagnosis of advanced cancer; weight loss greater than 10% from usual body weight; absence of severe hepatic or renal dysfunction (bilirubin greater than 3 mg/dl and/or creatinine greater than 2 mg/dl); and normal mental status. Patients with a known history of diabetes mellitus or those receiving corticosteroid therapy were ineligible. Patients with ascites or clinically significant edema were not entered to avoid confounding weight determinations. Patients were entered either prior to receiving systemic chemotherapy or when a new systemic therapy program was initiated

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Supported in part by Grant CA37320 from the National Cancer Institute, NIH; Grant RD-163 from the American Cancer Society; and Grant RR-00425 (General Clinical Research Center) from the NIH.

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Accepted for publication September 9, 1986.

for disease progression. Measurable disease parameters were not required, and concurrent chemotherapy was permitted. Both initial and repeat assessment of all study parameters, however, were conducted at least 2 days before and 4 weeks after chemotherapy administration.

After informed consent was obtained, patients underwent an initial assessment of nutritional parameters, including caloric intake as described below. Patients subsequently were treated with capsules containing hydrazine sulfate (60 mg) or placebo which were prepared by Anabolic, Inc. (Irvine, California). Hydrazine sulfate was given under IND 17, 671 from the Food and Drug Administration (FDA) (obtained by Dr. Chlebowski). All institutional requirements for human subjects review were met. The treatment program consisted of an escalating schedule of capsules containing either hydrazine sulfate or placebo until the full dosage of 60 mg, 3 times/d given before meals, was reached beginning on the 8th day. This program was based on the extensive Russian experience.¹⁵ Patients were contacted weekly to assess compliance and kept daily compliance diaries. The validity of daily compliance diaries was checked against intake based on returned prescription bottles. Following 30 days of either agent, the assessment of body weight, caloric intake, and other parameters was repeated.

During the initial and repeat evaluation, all patients received determination of body weight measured on the same printing scale; anthropometrics, including tricep skinfold thickness, mid-arm muscle circumference, and serum albumin; caloric intake using a 24-hour dietary recall history obtained by nutritionists and computer analyzed to give protein, carbohydrate, fat, and energy contents of the diet. Expected caloric intake was normalized for each patient by weight based on a calculated recommended daily allowance (RDA). Toxic effects of treatment and influence on appetite were determined by questionnaire.

In a subset of 14 patients, blood samples for hydrazine sulfate circulatory levels were obtained as a morning sample taken at least 9 hours from the last oral dose following 30 days of treatment. Hydrazine sulfate levels were measured using a defined^{16,17} spectrofluorometric assay in which reaction of hydrazine sulfate with dimethylaminobenzaldehyde produces a colored derivative. Fluorescence was subsequently determined in an Aminco Bowman (Silver Spring, MD) spectrophotofluorometer with an excitation wavelength of 466 nm and emission wavelength of 546 nm.

All patients were given defined, uniform dietary counselling based on nutritional status at entry to insure comparability of dietary information available to patients on hydrazine or placebo treatment. The nutritional guidelines all patients were provided with were designed to duplicate a routine clinical dietary assessment that would be expected to be a component of a cancer patient's standard

TABLE 1. Pretreatment Characteristics of Cancer Patients Receiving Hydrazine Sulfate or Placebo

	Treatment received	
	Hydrazine	Placebo
Number entered	71	30
Age in years		
Median	56	59
Range	32-77	36-77
Sex (% Male)	61%	65%
Disease type		
Lung	46	15
Colon	13	4
Other breast	4	3
Esophagus	2	3
Nasopharyngeal	3	1
Hepatocellular	1	2
Ovarian	2	1
Prostate	0	1
Performance score		
(0 or 1)	14%	23%
(2 or 3)	86%	77%
Nutritional status		
% Weight loss (mean)	17%	14%
Caloric intake		
≥90% of RDA	39%	41%
<90% of RDA	61%	59%
Albumin gm/dl (Mean)	3.4	3.3
Concurrent chemotherapy	78%	74%

RDA: recommended daily allowance.

clinical management. Enteral tube feedings or parenteral nutritional support was not given any patient while on study.

A total of 101 patients with advanced cancer underwent initial evaluation. Sixty-one consecutive patients (including all 30 patients given placebo and 31 given hydrazine) were randomly assigned treatment in a double-blind fashion with treatment assignment based on published random-number tables. An additional 40 patients received hydrazine sulfate and represented a consecutive series of patients seen in the Clinical Research Center meeting entry criteria for the trial. Statistically significant differences between hydrazine and placebo groups relative to pretreatment clinical factors were sought using chi square contingency table analyses and Student's *t* test. The statistical differences between hydrazine and placebo treatment were determined using the two-group *t* test.

Results

A total of 101 patients with a variety of advanced cancers underwent initial evaluation. Patients receiving hydrazine sulfate or placebo were comparable with respect to tumor type, age, sex, performance score, nutritional parameters and chemotherapy experience (Tables 1 and 2). The compromised nutritional status of the study pop-

TABLE 2. Concurrent Chemotherapy of Cancer Patients Receiving Hydrazine Sulfate or Placebo According to Disease Type

Chemotherapy given	Study arm	
	Hydrazine	Placebo
Lung cancer (n)	46	15
PACcO	15	4
PVB	12	7
ACcO	9	2
ACO	2	0
No chemotherapy	8	2
Colon cancer (n)	13	4
5-FU	2	1
5-FU + vitamin K	7	1
No chemotherapy	4	2
Other disease sites (n)*	12	11
No chemotherapy	4	3

P: cisplatin (Platinol); A: doxorubicin, (Adriamycin); C: cyclophosphamide; c: CCNU; O: vincristine (Oncovin); 5-FU: 5-fluorouracil; V: vinblastine; B: bleomycin; 5-FU + vit K: 5-fluorouracil plus vitamin K₃ (Synkavite).

* The patients with other disease sites received a variety of regimens which included cisplatin in 62% and 50% of instances for the hydrazine and placebo group, respectively.

ulation is demonstrated by the 16% average weight loss experienced by the overall population. Of this advanced disease population with weight loss, 58 patients were able to complete repeat evaluations after 30 days of treatment (41 were given hydrazine; 17, placebo). Early disease progression and/or death accounted for almost all cases not having repeat study. Only two patients refused repeat evaluation.

The influence of 30 days of hydrazine sulfate or placebo therapy on study parameters for all entered patients who underwent repeat evaluation is outlined in Table 3. Weight was maintained or increased in a higher proportion of patients receiving hydrazine sulfate compared to placebo therapy (83% versus 53%, respectively; $P < 0.05$). The use of weight loss as a study parameter was not compromised by the development of ascites or significant edema, as this did not occur in any patient over the 30 day period of

TABLE 3. Influence of 30 Days of Hydrazine Sulfate or Placebo on Nutritional Status of Cancer Patients With Weight Loss

	Hydrazine n = 41*	Placebo n = 17
Weight maintained or increased (>2.5 kg)	83%†	53%
Improvement in appetite	63%†	25%
Caloric intake increased (>10% over baseline)	51%	37%
Increased caloric intake associated with weight gain (>2.5 kg)	81%†	53%

* Number completing initial and repeat study.

† $P < 0.05$ hydrazine compared to placebo group.

observation. Anthropometrics were unchanged over the 30-day study period. Caloric intake was only slightly higher in the hydrazine treated population. When all patients experiencing an increase in caloric intake were considered, however, weight gain was seen in a significantly higher proportion of patients receiving hydrazine sulfate while increasing caloric intake compared with those who increased caloric intake while receiving placebo. The results using hydrazine sulfate were closely comparable in the 31 patients entered as part of the randomized trial when compared with the 40 patients added as a consecutive series. The results for the patients receiving hydrazine or placebo who were entered as part of the randomized trial were: weight maintained or increased, 71% versus 53%; improvement in appetite, 63% versus 25%; caloric intake increased, 69% versus 37%; and increased caloric intake associated with weight gain, 77% versus 53% for the hydrazine versus placebo patients respectively. In addition, results in groups receiving or not receiving concurrent chemotherapy reflected those obtained in the entire group.

Thirty-five patients with cancer other than small cell lung cancer (the predominant tumor type studied) completed serial evaluation, with 26 receiving hydrazine sulfate and nine receiving a placebo. In the lung cancer patients, weight maintenance or increase was achieved in 83% of those receiving hydrazine sulfate compared with 33% of those receiving the placebo.

The short term hydrazine sulfate regimen used in this trial was well tolerated by study participants. Compliance forms were returned by 90% of patients who completed repeat evaluations, and indicated that 95% of the scheduled dose was taken by the study population completing 30 days of therapy. The mean maintenance plasma hydrazine sulfate levels obtained from a subset of 14 patients ranged from 0 to 89 ng/ml with a mean value of 45 ± 16 ng/ml. Clinical toxicity of patients receiving hydrazine sulfate was limited largely to mild to moderate nausea and lightheadedness with 71% of patients reporting no toxic effects from hydrazine use (Table 4). Treatment was discontinued for toxic effects in 10% of patients receiving hydrazine; while 6% of patients receiving placebo had treatment stopped for "toxic effects." Significantly, parasthesias or hypoglycemic symptoms were not reported by any patient receiving hydrazine in this trial.

Discussion

Short-term administration of hydrazine sulfate was better than a placebo in maintaining body weight and improving appetite in patients with advanced cancer in the current clinical experience. The weight effect apparently resulted from an increase in the effectiveness of the ingested calories, since a higher proportion of patients

who increased their caloric intake on hydrazine were able to maintain or improve their body weight. The association that we have reported¹⁸ between weight maintenance and improved glucose metabolism in hydrazine-treated cancer patients suggests that interruption of abnormal metabolic pathway function may underlie the improved nutritional status seen with hydrazine sulfate in the current trial. If this hypothesis can be confirmed, hydrazine sulfate could represent one of a new class of metabolic/hormonal agents¹⁹⁻²¹ directed at influencing the abnormal metabolism seen frequently in patients with cancer.

No prior clinical experience with hydrazine sulfate in cancer patients has prospectively evaluated caloric intake or included a placebo control population. Single-arm studies involving 348 Russian and 84 American patients with cancer have emphasized subjective parameters.^{15,22} In the American experience, Gold²² reported that 70% of the treatment group demonstrated subjective improvement, including increased appetite with either weight gain or cessation of weight loss, increased strength and improved performance status, or decreased pain, as measured by need for analgesics. In the Russian experience, Gershonovich^{15,23} reported that 50% of patients receiving hydrazine sulfate as their sole therapeutic intervention achieved moderate or marked improvement in cachexia with associated favorable symptomatic effects on appetite and pain. Not all clinical studies of hydrazine sulfate have shown benefit. In three small trials of hydrazine sulfate (all entering less than 30 patients) where reduction in tumor size was used as a major therapeutic endpoint, little benefit was reported.²⁴⁻²⁶ The clinical effects of hydrazine sulfate on body weight observed in the current study in conjunction with the metabolic effects of hydrazine that we reported in 1984¹² now provides a strong rationale for further studies designed to assess the impact of hydrazine sulfate on clinical outcome in defined cancer populations.

Surprisingly, thirty-seven percent of weight-losing cancer patients given placebo in this trial increased their caloric intake by more than 10%, and 53% of the placebo group maintained or increased their body weight over the 1-month observation period. This result in the placebo population may have been related to the nutritional counseling that was given in identical fashion to patients on both treatment arms in this study. Placebo controls clearly are important in trials designed to alter and assess nutritional parameters in cancer populations.

The study protocol employed in our trial was not designed to assess the influence of hydrazine sulfate on tumor growth characteristics. The short 30-day period of treatment and entry criteria preclude assessment of hydrazine sulfate influence on this parameter. Almost all of our patients with advanced solid tumors refractory to initial therapy, however, demonstrated no change in tumor dimensions during the 1-month period of observation.

TABLE 4. Patient Tolerance of Hydrazine Sulfate or Placebo Treatment

	% of Patients Treated	
	Hydrazine	Placebo
No toxic effects	71%	84%
Nausea and vomiting		
Mild	12%	12%
Moderate	5%	0%
Light-headedness	17%	6%
Treatment discontinued for toxic effects	10%	6%

The relative lack of toxicity of short-term hydrazine sulfate administration in a 60 mg 3 times/d schedule to a large cancer population receiving other concurrent chemotherapy treatment was noteworthy. In the previous limited clinical experience,^{15,22,23} only one report has emphasized significant toxicity; Ochoa and coworkers²⁴ reported a 50% incidence of polyneuritis associated with hydrazine sulfate use in a 29-patient experience. In three trials^{15,22,25} and the present report, polyneuritis was seen in less than 1% of the more than 500-patient cumulative experience. The lack of toxicity in the current experience can be documented further by the good compliance reported by the patients in their diaries. The latter result is interesting considering the somewhat wide range of hydrazine sulfate maintenance circulatory levels observed in the pharmacokinetic component of this trial. However, these results are consistent with developing pharmacokinetic information regarding the half-time of oral hydrazine sulfate administration.¹⁷ These data suggest that future clinical trials involving hydrazine sulfate should include determination of chronic circulatory levels to assess hydrazine sulfate bioavailability and permit correlation with metabolic, nutritional and clinical endpoints.

Conclusion

This experience with hydrazine sulfate in an advanced cancer population points to a potential role for this agent in maintaining weight in patients with cancer cachexia. Whether maintenance of body weight under these conditions will be associated with improvement in important clinical outcome variables and overall survival will require future prospective, long-term, placebo-controlled evaluation in cancer populations with less advanced disease given defined systemic therapy. Such studies in the non-small cell lung cancer population are currently in progress.

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Oncology 32: 1-10 (1975)

Use of Hydrazine Sulfate in Terminal and Preterminal Cancer Patients: Results of Investigational New Drug (IND) Study in 84 Evaluable Patients

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Key Words. Hydrazine sulfate therapy in advanced cancer patients · Treatment of advanced human cancer with anti-gluconeogenic drugs · Interruption of cancer cachexia as a means of cancer chemotherapy · Interruption of gluconeogenesis as a means of cancer chemotherapy

Abstract. In a series of 84 various evaluable disseminated cancer patients treated with hydrazine sulfate as a result of a pharmaceutical-sponsored investigational new drug (IND) study, it was found that 59/84 or 70 % of the cases improved subjectively and 14/84 or 17 % improved objectively. Subjective responses included increased appetite with either weight gain or cessation of weight loss, increase in strength and improved performance status and decrease in pain. Objective responses included measurable tumor regression, disappearance of or decrease in neoplastic-associated disorders and long-term (over 1 year) 'stabilized condition'. Of the overall 59 subjective improvements 25 (42 %) had no concurrent or prior (within 3 months) anticancer therapy of any type. Of the 14 objective improvements 7 (50 %) had no concurrent or prior anticancer therapy. Of the remaining cases in which there was either concurrent or prior anticancer therapy, improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Duration of improvement was variable, from temporary to long-term and continuing. Side effects were mild, comprising for the most part low incidences of extremity paresthesias, nausea, pruritis and drowsiness; there was no indication of bone marrow depression.

Hydrazine sulfate has been used as an investigational new drug (IND) for over 1 year in the treatment of advanced cancer. Its proposed mechanism of action is as a gluconeogenic blocking agent at the phosphoenolpyruvate carboxykinase (PEP CK) reaction, attenuating host energy loss as a result of increased gluconeogenesis in cancer and therefore interrupting the *systemic* cycle of *tumor-energy gain-host-energy loss* (tumor growth-host cachexia) (1, 2). Early reports indicated that hydrazine sulfate, administered orally to advanced cancer patients, resulted in marked subjective and objective improvements (3), subjective improvements including increase in appetite, cessation of weight loss and/or

weight gain, improved performance status, and decrease in pain; objective improvements included measurable reduction in tumor size and reduction in or disappearance of neoplastic-associated disorders (effusions, jaundice, etc.). Duration of improvements was reported as variable and side effects, minimal. In further reports (4), in which hydrazine sulfate was used in conjunction with conventional chemotherapy in patients with disseminated neoplasia, it was unclear as to which type of therapy resulted in the reported subjective and objective improvements. The present report, undertaken as a pharmaceutical-sponsored IND study and representing a series of 84 evaluable cases of various terminal and preterminal cancer patients, indicates a high degree of anticancer activity in patients treated with hydrazine sulfate alone.

Procedures and Protocols

Physician selection. This study was the result of separate inputs of many clinicians – oncologists as well as others – whose participation was under pharmaceutical IND sponsorship. As such, this study is designated as ‘uncontrolled’.

Patient selection. Patients with any type of disseminated neoplasia, who no longer responded to chemotherapy and/or radiation, were considered eligible for hydrazine sulfate therapy. A minimum prognosis of 2 months was recommended.

Drug and protocol. The drug consisted of 100 % purity hydrazine sulfate mixed with an inert starch in capsular form (pharmaceutical IND preparation) for oral administration. Protocol of drug administration was as follows: 60 mg q.d. × 4; 60 mg b.i.d. × 4; then 60 mg t.i.d. as maintenance. In patients weighing less than 50 kg, dosages were halved (i.e., 30 mg q.d. × 4; 30 mg b.i.d. × 4; then 30 mg t.i.d.). In the event that a b.i.d. schedule produced satisfactory results, this dosage schedule was maintained at the clinician’s discretion. In no event was a single dosage ever to exceed 60 mg.

Concurrent anticancer medication. The continuing use of concurrent anticancer medication was acceptable if it was no longer producing a demonstrable anticancer effect by itself.

Data presentation. A 4-sheet data page (‘Patient Report Form’) was required to be completed by the clinician during the course of treatment of each patient. These data sheets included the following information: detailed history, site of tumor and metastases, prior treatments (defined in this study as any type of anticancer therapy given within 3 months of the initiation of hydrazine sulfate therapy; prior treatment data included dates of therapy, types and quantitation), concurrent medications, performance status evaluation, objective tumor size and site evaluations, subjective observation ratings and check list, laboratory data, clinician’s statement of patient evaluation prior to hydrazine sulfate therapy, clinician’s statement of evaluation of results of hydrazine sulfate therapy, clinician’s evaluation of side effects of hydrazine sulfate therapy, and clinician’s signature.

Criteria for designation as ‘improvement’. Designation of subjective improvements was made on the basis of improvements indicated in the subjective observations rating check list and/or affirmation of improvement in the clinician’s statement under ‘clinician evaluation’ section. In general a subjective improvement was based on a quantitatively measurable or estimable parameter such as strength (number of hours ambulatory, quality of ambulation, etc.), appetite (food intake), weight (scale measurement) and pain (quantitative need for analgesics). Objective improvements were designated on the basis of measurable reduction in

tumor size, long-term (1 year or more) 'stabilized condition' in a previously rapidly growing neoplasm, and disappearance of or reduction in neoplastic-associated disorders. Each case in this category was to be supported by related laboratory measurements, where possible.

Criteria for designation as 'nonevaluable'. Cases were deleted from evaluation for any of the following reasons: (a) inadequate prognosis: patient survival of less than 3 weeks; (b) inadequate drug trial: drug trial of less than 3 weeks; (c) insufficient data submitted on Patient Report Form: no evaluation possible, and (d) concurrent treatment with newly initiated cytotoxic chemotherapy: patient response nonevaluable.

Results

Of a total number of 158 cases submitted in the study, 84 were evaluable and 74 nonevaluable. Of the evaluable cases 14 (17%) were categorized as 'objective (and subjective) improvement', 45 (54%) as 'subjective improvement only', and 25 (30%) as 'no improvement'. The indicated overall improvement

Table 1. Categorization of evaluable cases in Investigational New Drug study of hydrazine sulfate

Site and/or type of primary tumor	Objective and subjective improvements	Subjective improvement only	No improvement	Total cases
Brain (astro, glio)	2	0	0	2
Breast (all)	2	6	2	10
Colorectal-gastric	2	12	8	22
Gallbladder	1	0	0	1
Hodgkins, stage IV	0	0	2	2
Liver (primary)	0	0	1	1
Lung (all)	2	11	2	15
Melanoma	0	1	2	3
Neurosarcoma (neck)	0	1	0	1
Ovary (all)	1	3	1	5
Pancreas	1	4	3	8
Primary unknown	0	2	0	2
Prostate	0	1	2	3
Squamous cell (neck)	0	1	0	1
Testis	0	1	0	1
Tonsil (palatine)	1	0	0	1
Urinary bladder, ureter	0	1	2	3
Uterus (cervix)	1	1	0	2
Uterus (endometrial)	1	0	0	1
Total	14	45	25	84

Table II. Nonevaluable cases: reasons for exclusion from evaluation

Inadequate prognosis survival time, weeks			Inadequate drug trial, weeks on drug			Insufficient data	New concurrent cytotoxic chemotherapy	Total cases
0-1	1-2	2-3	0-1	1-2	2-3			
11	11	9	8	6	11			
31			25			15	3	74

rate was 59/84 cases, or 70%. Of the nonevaluable cases, 31 (42%) were included under 'inadequate prognosis', 25 (34%) under 'inadequate drug trial', 15 (20%) under 'insufficient data', and 3 (4%) under 'newly initiated cytotoxic chemotherapy'. Categorization of evaluable and nonevaluable cases is given in tables I and II, respectively.

'Improvements'

Improvements were noted in tumors from almost all of the 19 reported sites of origin. No particular site of origin or tumor type was 'most susceptible' to hydrazine sulfate therapy, although the largest number of cases came from colorectal and lung carcinoma, which reflects the general incidence of these diseases in the population. The duration of improvement was variable, being reported from very temporary (1 week) to in excess of 1 year and continuing. It was possible to obtain follow-up reports in only less than half of the improved cases.

Objective responses. Of the 14 reported objective responses, 7 (50%) showed measurable tumor regression; 2 of these were accompanied by a disappearance of or reduction in neoplastic-associated disorders (effusions, jaundice, etc.). An additional 2 (14%) of the 14 cases were classified as long-term 'stabilized condition', both of which represented preterminal lung cancers whose disease had been rapidly progressive prior to hydrazine sulfate therapy. They are currently both alive and well 17 and 18 months after initiation of hydrazine sulfate therapy, respectively; neither are on any kind of concurrent anticancer therapy. The remainder of the 5 (36%) cases were classified as objective responses on the basis of amelioration of neoplastic-associated disorders, accompanied by marked subjective improvements. (In this regard all 14 cases showed subjective improvements.) All objective responses were also accompanied by tumor-related laboratory improvements, where measured.

Subjective responses. A total of 45 cases displayed subjective improvements only; this number, added to the foregoing 14 cases, gave a combined total of 59 subjectively improved cases. 48 (81%) of these showed an increase in appetite

Table III. Response analysis in improved cases

	No con- current or prior anti- cancer therapy	Concur- rent anti- cancer (incl. cyto- toxic) therapy	Concur- rent steroid therapy only	Concur- rent steroid and prior cyto- toxic therapy	Concur- rent steroid and prior radiation therapy	Prior cyto- toxic therapy	Prior steroid therapy	Prior radia- tion therapy	Total cases
Objective responses	7 (50 %)	3 (21 %)	1 (7 %)	—	1 (7 %)	—	1 (7 %)	1 (7 %)	14
Subjective responses	18 (40 %)	17 (38 %)	5 (11 %)	1 (2 %)	—	3 (7 %)	—	1 (2 %)	45

with either weight gain or a cessation of weight loss. 48 (81 %) showed an improvement in performance status as measured by an increase in strength, ambulation or both. And 21 (36 %) showed a decrease in pain as measured by a reduced need for analgesics.

Ongoing concurrent (or prior) anticancer therapy. Various of the improved cases were treated with either steroids and/or cytotoxic chemotherapy and/or radiation, prior to initiation of hydrazine sulfate therapy, as indicated in table III. In all these cases the noted improvements occurred *after* the addition of hydrazine sulfate to the therapy. In regard to the objective responses 7 (50 %) of the 14 cases were treated with hydrazine sulfate alone, without concurrent or prior anticancer therapy of any type, while 7 (50 %) of the cases did receive concurrent or prior anticancer therapy. In the subjective-only responses, 18/45 or 40 % of the cases were treated only with hydrazine sulfate, without concurrent or prior anticancer therapy, while 27 of the cases (60 %) did receive concurrent or prior anticancer therapy.

'No Improvements'

Of the 25 'no improvement' cases 2 (8 %) expired within 3–4 weeks after initiation of hydrazine sulfate therapy; 2 (8 %) had very little information in their Patient Report Form so that actual categorization became difficult; 9 (36 %) had a drug trial of only 3–4 weeks, and 14 (56 %) had concurrent anticancer therapy which consisted of cytotoxic drugs, radiation, steroids or combinations thereof. In only 5 cases were these foregoing considerations not a factor, i.e., the patient had an adequate prognosis and drug trial, had no concurrent or prior anticancer therapy, and had sufficient information submitted on his Patient Report Form to support a categorization of 'no improvement'.

Nonevaluable Cases

The general breakdown of categories of the 74 nonevaluable cases is given above and in table II. Of a total of 31 of these cases excluded from evaluation because of inadequate prognosis (survival time), 11 died within 1 week of initiation of hydrazine sulfate therapy, 22 died within 2 weeks, and the full 31 died within 3 weeks. Of a total of 25 additional cases excluded from evaluation for reasons of inadequate drug trial, 8 were on drug for only 1 week or less, 14 were on drug for 2 weeks or less, and the full 25 were on drug for 3 weeks or less. Thus, of the 56 cases excluded from consideration for the foregoing two reasons, 19 had a survival time or drug trial of 1 week or less, 36 had a survival time or drug trial of 2 weeks or less, and the full number — 56 — had a survival time or drug trial of 3 weeks or less.

Side Effects

Side effects were determined on the basis of evaluable cases only and were in general mild. They comprised: *extremity paresthesias* (5 %); this condition was diminished or eliminated by a reduction of dosage and/or administration of pyridoxine hydrochloride (vitamin B₆) in excess of 25 mg daily; *nausea* (4 %), in most cases transient; nontransient nausea was eliminated by a reduction of dosage or withdrawal of medication for a period of several days, then reinstatement of treatment at lower dosage levels; *dry skin* or *transient pruritis* (3 %); *'dizziness'* (1 %); *'drowsiness'* (1 %); *possible thrombophlebitis* (1 %) (it was not known whether this condition was drug-related). The total evaluable cases showing side effects numbered 13/84 or an overall 15 %. There were no deaths attributable to hydrazine sulfate therapy, either in the evaluable or in the nonevaluable cases.

Discussion

It is important that a detailed analysis of a study of this nature include not only the obviously improved cases as a result of hydrazine sulfate administration, but also the nonimproved and nonevaluable cases. Such factors as poor patient and clinician selection as well as inadequate protocol planning, must be assessed as to their quantitative contribution to the latter two categories.

Nonimproved and Nonevaluable Cases

Lack of proper patient selection, via inadequate patient prognosis and inadequate drug trial, contributed heavily to the large number of nonevaluable and nonimproved cases. Minimum protocol-recommended prognosis was 2 months, yet as many as 31/74 or 42 % of the nonevaluable cases were so designated because of a survival time of 3 weeks or less, while in the nonimproved category

2/25 or 8 % of the cases had a survival time of only 3–4 weeks. In addition, as many as 25/74 or 34 % of the nonevaluable cases were so designated because of an inadequate drug trial (3 weeks or less), while 9/25 or 36 % of the nonimproved cases had a drug trial of only 3–4 weeks. Thus, in the nonevaluable category the number of combined inadequate prognosis and inadequate drug trial cases totaled 56/74 or 76 %, while in the nonimproved category the number of combined cases of 'borderline-acceptable' survival time and drug trial (3–4 weeks) totaled 11/25 or 44 %. Such large percentages, representing inadequate prognosis and inadequate drug trial, must be attributed chiefly to improper patient selection and not to the occasional miscalculations which arise in any study.

Lack of proper clinician selection was also an apparent factor in this study, manifest chiefly in those cases in which too little information was submitted. In the nonevaluable category as many as 15/74 or 20 % of the cases were so designated because of lack of sufficient information upon which to make an evaluation. Even in the nonimproved category 2/25 or 8 % of the cases had only a minimum of information submitted. Such numbers surely reflect a lack of interest or capability on the part of the clinician. (Indeed, inadequate patient selection itself may be a function of this type of clinician inadequacy.)

Poor protocol planning, manifest by the acceptability of concurrent anticancer therapy, also had a major input in these two categories. In the nonevaluable group 3/74 or 4 % of the cases were so designated because of newly initiated concurrent cytotoxic chemotherapy, rendering impossible any attributive evaluation of patient response. In the nonimproved group as many as 14/25 or 56 % of the cases had ongoing concurrent anticancer therapy which was no longer producing demonstrable clinical benefit, but which could, by virtue of its immunosuppressive and hematosuppressive effects, adversely affect or mask the results of any new drug concurrently administered. Clearly, the protocol was weakened by inclusion of any type of concurrent anticancer therapy whatsoever.

Thus, in retrospect many of the cases which fell into the nonevaluable and nonimproved categories should properly never have entered this study. This circumstance could have been obviated by better patient and clinician selection as well as by a 'tighter' protocol. It is hoped that a careful categorization in this study has dealt adequately with these factors.

Improved Cases

Despite the above-described considerations, a large number of clearly improved cases emerged in this study. This improvement, moreover, was the result of administration of hydrazine sulfate alone in a large percentage of the cases and was not influenced by any other mode of concurrent or prior anticancer therapy. Table III indicates that 50 % of the objectively improved cases (7/14) were on hydrazine sulfate alone, with no prior or concurrent anticancer therapy;

and 40 % (18/45) of the subjective-only responses were also the result of hydrazine sulfate therapy alone. This constitutes strong *prima facie* evidence indicating hydrazine sulfate to be a clinically active anticancer agent in itself. It is important to remember that even in those cases which received concurrent or prior anticancer therapy, the noted improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Thus, whether as a sole agent or in combination with other agents, administration of hydrazine sulfate to advanced cancer patients is linked to marked anticancer responses.

Moreover, hydrazine sulfate is apparently not a 'tumor-specific' agent, as can be seen from table I. Virtually all types of cancer — especially those which ultimately promote a degree of host cachexia — are apparently susceptible to its actions. Reports, in addition to those of this study, which have reached this laboratory, indicate that the spectrum of disease beneficially affected by hydrazine sulfate extends to cancers arising from all organ systems and/or tissues in the body. The most dramatic responses reported to date have been those with primary lung neoplasms, although this observation may prove to be premature as more and earlier cases are reported.

The duration of improvement has been unpredictable, but has generally been longer in those cases responding objectively (as well as subjectively). Some of the responses have been of very short duration. But others have been quite lengthy. To date three cases in this study — two primary lung and one ovarian — are alive 17, 18 and 21 months after institution of hydrazine sulfate therapy alone, respectively; all three were previously considered terminal or preterminal. Preliminary indications suggest that the improvements brought about by hydrazine sulfate therapy — whether objective or subjective — have been accompanied by extension in survival time and that the quality of this survival time was high: patients who had obtained objective response and/or increased appetite, strength and decreased pain as a result of hydrazine sulfate therapy, were reported to have been restored to a more positive orientation toward living.

The duration of improvement may also be related to the degree of advancement of the disease. The patients in this study were in general in the very latest stages of disease, yet there were many improvements, some of which were marked. However, it is generally regarded that any modality of anticancer therapy has its best chances of success when used *early* in the course of disease. And this is probably true of hydrazine sulfate. There would seemingly be no disadvantage in instituting hydrazine sulfate therapy early in the course of disease, especially in those cases where the ultimate clinical course is virtually unaffected by any known therapeutic modality. Moreover, since the toxicity of hydrazine sulfate is apparently of a low order of magnitude, unlike many of the cytotoxic drugs whose 'side effects' can produce extreme patient discomfort and death, it would seem prudent to investigate the effect of this drug on early patients, rather than use it at the very last stages as a 'resurrective' type of therapy. If

positive responses can be obtained in terminal patients — as indicated in this study — it seems only reasonable that a greater degree of positive response could be expected in early patients, as is the case with many other anticancer modalities.

Side Effects

The side effects of hydrazine sulfate are indeed of a very minor nature as reported in this study, with the possible exception of 'torpidity' or 'drowsiness' which had less than a 1 % incidence and occurred only in very advanced bedridden case(s). The most frequent side effect, occurring usually after the 6th week of therapy, appears to be the development of mild extremity paresthesias, particularly of the fingers and toes. This condition reportedly can be diminished or eliminated by dosage reduction and/or addition of vitamin B₆ (in excess of 25 mg daily) to the regimen. Other side effects such as nausea, pruritis, etc., appear to be transient in nature and not a clinical problem, with few exceptions. In general, since hydrazine sulfate is not a cytotoxic agent, there have been none of the severe side effects of these drugs reported with its use, and this is especially true of hematopoietic-suppressive effects. Hydrazine sulfate does not depress the bone marrow. On the contrary, several of the cases of this study with advanced prostatic or breast cancer showed net *elevations* in hemoglobin, hematocrit and platelets within 2 weeks of initiation of treatment. This observation has been confirmed in many case reports not a part of this study and thus is in contrast to the cytotoxic drugs, one of the prime limitations of which are their hematosuppressive effects. Finally, hydrazine sulfate has not been demonstrated clinically to possess immunosuppressive properties, although this must await verification by further basic studies.

Concluding Remark

Hydrazine sulfate therapy is a new type of chemotherapy. Its clinical use at present represents a *beginning*. Whether a study with any new drug is positive or negative, it must always be evaluated in terms of the 'state of the art'. Hydrazine sulfate represents the *first* of a class of new agents designed to interrupt host participation in cancer. Other agents in this class now in development may prove to be far superior to hydrazine sulfate. In addition, adjunctive agents to hydrazine sulfate therapy may also prove to be very important. In this respect it has already been learned by this laboratory that administration of a substance interfering with triglyceride synthesis, can greatly potentiate the anticancer action of hydrazine sulfate (paper in preparation). For these types of reasons it must be emphasized that the clinical potential of hydrazine sulfate-like drugs in cancer has only just begun to be explored, and much further work lies ahead before a more comprehensive understanding of their ultimate anticancer potential becomes clear.

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Oncology **32**: 11-20 (1975)

Primary C-Cell Hyper

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Key Words. Thyroid C cells · carcinoma

Abstract. The electron mic
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Introduction

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