Bailey GS, Hendricks JD, Shelton DW, et al. Enhancement of carcinogenesis by the natural anti-carcinogen indole-3-carbinol. *J Natl Cancer Inst.* 1987; 78:931-934.

Bradlow HL, Michnovicz JJ, Wong GYC, et al. Long term responses of women to indole-3-carbinol or a high fiber diet. *Cancer Epidemiol Biomarkers Prev.* 1994; 3:591-595.

Bradlow HL, Sepkovic DW, Telang NT, Osborne MP. Multifunctional aspects of the action of indole-3-carbinol as an antitumor agent. *Ann NY Acad Sci.* 1999; 889:204-213.

Cover CM, Hsieh SJ, Cram EJ, et al. Indole-3-carbinol and tamoxifen cooperate to arrest the cell cycle of MCF-7 human breast cancer cells. *Cancer Res.* 1999; 59:1244-1251.

Grubbs CJ, Steele VE, Casebolt T, et al. Chemoprevention of chemically-induced mammary carcinogenesis by indole-3-carbinol. *Anticancer Res.* 1995; 15:709-716.

He Y-H, Freisen MD, Ruch RJ, Schut HAJ. Indole-3-carbinol as a chemopreventive agent in 2-amino-1-methyl-6-phenylimidazo [4,5-*b*] pyridine (PhIP) carcinogenesis: inhibition of PhIP-DNA adduct formation, acceleration of PhIP metabolism, and induction of cytochrome P450 in female F344 rats. *Food Chem Toxicol.* 2000; 38:15-23.

Kim DJ, Han BS, Ahn B, et al. Enhancement by indole-3-carbinol of liver and thyroid gland neoplastic development in a rat medium-term multiorgan carcinogenesis model. *Carcinogenesis.* 1997; 18:377-381.

Michnovicz JJ, Bradlow HL. Induction of estradiol metabolism by dietary indole-3-carbinol in humans. *J Natl Cancer Inst.* 1990; 50:947-950.

Niwa T, Swaneck G, Bradlow HL. Alterations in estradiol metabolism in MCF-7 cells induced by treatment with indole-3-carbinol and related compounds. *Steroids.* 1994; 59:523-527.

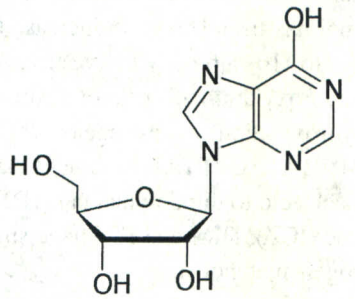
Wong GYC, Bradlow HL, Sepkovic DW, et al. A dose-ranging study of indole-3-carbinol for breast cancer prevention. *J Cell Biol.* 1988; 28:111-116.

Zeligs MA. Diet and estrogen status: the cruciferous connection. *J Med Food.* 1998; 1:67-82.

Inosine

DESCRIPTION

Inosine is a purine ribonucleoside widely found in plants, animals and other forms of living matter. It is comprised of the purine base hypoxanthine and the sugar D-ribose. The structural formula is:



Inosine

Inosine, in the form of its nucleotide, inosine 5′-monophosphate (inosinate), is the precursor of adenosine monophosphate (AMP) and guanosine monophosphate (GMP) in the *de novo* biosynthesis of purine nucleotides. It is also an intermediate in the so-called salvage pathway of purine nucleotide synthesis, and it is an intermediate in the degradation of purines and purine nucleosides to the purine end-product, uric acid. Inosine is also found as a minor nucleoside in transfer RNA.

Disodium inosinate is commonly used in foods for flavor enhancement and comprises a significant proportion of the dietary intake of inosine. Inosine itself has been used as a pharmaceutical agent. Some time ago, Trophicardyl was used in France for the treatment of cardiovascular conditions, including ischemia, cardiomyopathy and arrythmias. The active drug was inosine. In Russia, Riboxin, again inosine, was and is still used for the treatment of similar disorders. Inosine pranobex (Isoprinosine), a delivery form of inosine, is an orphan drug indicated for the treatment of subacute sclerosing panencephalitis. This drug is also thought to have immunomodulatory activity.

Inosine is also known as hypoxanthine riboside, 9-beta-D-ribofuranosylhypoxanthine and hypoxanthosine. It is abbreviated I.

ACTIONS AND PHARMACOLOGY

ACTIONS

Inosine may have neuroprotective, cardioprotective, anti-inflammatory and immunomodulatory activities.

MECHANISM OF ACTION

Inosine has been found to have potent axon-promoting effects *in vivo* following unilateral transection of the corticospinal tract of rats. The mechanism of this action is unclear. Possibilities include serving as an agonist of a nerve growth factor-activated protein kinase (N-Kinase), conversion to cyclic nucleotides that enable advancing nerve endings to overcome the inhibitory effects of myelin, stimulation of differentiation in rat sympathetic neurons,

augmentation of nerve growth factor-induced neuritogenesis and promotion of the survival of astrocytes, among others.

The mechanism of inosine's possible cardioprotective effect is similarly unclear. Inosine has been reported to have a positive inotropic effect and also to have mild coronary vasodilation activity. Exogenous inosine may contribute to the high-energy phosphate pool of cardiac muscle cells and favorably affect bioenergetics generally. Inosine has also been reported to enhance the myocardial uptake of carbohydrates relative to free fatty acids as well as glycolysis.

In cell culture studies, inosine has been found to inhibit the production, in immunostimulated macrophages and spleen cells, of the proinflammatory cytokines, tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, interleukin (IL)-12, macrophage-inflammatory protein-1 alpha and interferon (IFN)-gamma. It also suppressed proinflammatory cytokine production and mortality in a mouse endotoxemic model. These actions might account for the possible immunomodulatory, anti-inflammatory and anti-ischemic actions of inosine.

PHARMACOKINETICS

Ingested inosine is absorbed from the small intestine, from whence it is transported via the portal circulation to the liver. In the liver, inosine may be catabolized by a series of reactions culminating in the production of uric acid and also may be metabolized to adenine- and guanine-containing nucleotides. Inosine not metabolized in the liver is transported via the systemic circulation and distributed to various tissues of the body, where it is metabolized in similar fashion as in the liver. Uric acid, the purine end-product of inosine catabolism, is excreted in the urine.

INDICATIONS AND USAGE

The primary popular claim made for inosine, that it enhances exercise and athletic performance, is refuted by the available research data. There is some preliminary evidence that inosine may have some neurorestorative, anti-inflammatory, immunomodulatory and cardioprotective effects.

RESEARCH SUMMARY

In a double-blind, placebo-controlled, cross-over study of nine highly trained endurance runners, 6 grams daily of inosine failed to demonstrate any benefit in various exercise tests, including a three-mile treadmill run. By one of the measures used, placebo was significantly superior to inosine.

In another placebo-controlled study, inosine again failed to confer any advantage over placebo in 10 competitive male cyclists, as measured by tests of aerobic and anaerobic cycling performance. Here too, inosine was actually inferior to placebo under some test conditions, suggesting, the researchers concluded, that it might have an ergolytic effect.

Preliminary research has suggested that inosine can suppress proinflammatory cytokine production and mortality in a mouse endotoxemic model and that it has some cardioprotective effects in an animal model of ischemic heart. This was associated with an observed inosine-linked increase in glycolytic activity and improved energy production.

Inosine has also recently shown neurorestorative effects in the rat corticospinal tract after injury. It had previously been shown to induce axon outgrowth from primary neurons in culture. The more recent *in vivo* study encouraged the researchers to hope that inosine "might help to restore essential circuitry after injury to the central nervous system." More research is needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Supplemental inosine is contraindicated in those with a history of gouty arthritis with acute attacks. Known hypersensitivity to an inosine-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid supplemental inosine.

Those with a history of hyperuricemia should be extremely cautious about use of inosine.

ADVERSE REACTIONS

Mild gastrointestinal symptoms, such as abdominal discomfort and nausea, have occasionally been reported.

OVERDOSAGE

No reports of overdosage.

DOSAGE AND ADMINISTRATION

No typical doses. Doses of 5 to 10 grams daily were used in the above-reported studies of the effects of inosine on athletic performance.

LITERATURE

Benowitz LI, Goldberg DE, Madsen JR, et al. Inosine stimulates extensive axon collateral growth in the rat corticospinal tract after injury. *Proc Natl Acad Sci.* 1999; 96:13486-13490.

Hasko G, Kuhel DG, Nemeth ZH, et al. Inosine inhibits inflammatory cytokine production by a posttranscriptional mechanism and protects against endotoxin-induced shock. *J Immunol.* 2000; 164:1013-1019.

Korotkov AA, Zhorzholiani TD, Chkheidze LG, Shalamberidze DN. [Effect of inosine after early infusion of contrykal and heparin in various hemodynamic types of acute myocardial ischemia.] [Article in Russian.] *Kardiologiia.* 1998; 28:91-94.

Lewandowski ED, Johnston DL, Roberts R. Effects of inosine on glycolysis and contracture during myocardial ischemia. *Cir Res.* 1991; 68:578-587.

Mc Naughton L, Dalton B, Tarr J. Inosine supplementation has no effect on aerobic or anaerobic cycling performance. *Int J Sports Nutr.* 1999; 9:333-334.

Milano S, Dieli M, Millott S, et al. Effect of isoprinosine on IL-3, IFN-gamma and IL-4 production *in vivo* and *in vitro*. *Int J Immunopharmacol.* 1991; 13:1013-1018

Renoux G, Renoux M, Guillaumin J-M. Isoprinosine as an immunopotentiator. *J Immunopharmacol.* 1979; 1:337-356.

Starling RD, Trappe TA, Short KR, et al. Effect of inosine supplementation on aerobic and anaerobic cycling performance. *Med Sci Sports Exerc.* 1996; 28:1193-1198.

Williams MH, Kreider RB, Hunter DW, et al. Effect of inosine supplementation on 3-mile treadmill run performance and VO_2 peak. *Med Sci Sports Exec.* 1990; 22:517-522.

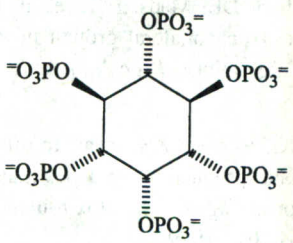
Zimmer HG. Effect of inosine on cardiac adenine nucleotide metabolism in rats. *Adv Myocardiol.* 1985; 6:173-183.

Inositol Hexaphosphate

DESCRIPTION

Inositol hexaphosphate, also known as phytate, is a component of most cereal grains and seeds, occurring in conjunction with plant fiber, and is a source of *myo*-inositol in the diet. Inositol hexaphosphate is responsible for storing more than 80 percent of the total phosphate in cereals and legumes. Phytate has strong chelating power for doubly charged metal ions, such as magnesium, calcium and zinc. Some studies suggest that phytate may slow tumor growth rates.

Inositol hexaphosphate, in addition to being known as phytate, is known as *myo*-inositol hexaphosphate, and *myo*-inositol 1,2,3,4,5,6-hexakisphosphate. Inositol hexaphosphate is abbreviated as $InsP_6$ and sometimes as IP-6. The structural formula is:



Inositol hexaphosphate

ACTIONS AND PHARMACOLOGY

ACTIONS

Inositol hexaphosphate is a putative antiproliferative agent and may have antioxidant activity.

MECHANISM OF ACTION

Some speculate that inositol hexaphosphate's possible antiproliferative activity is due to its chelating divalent cations which may be important for tumor growth. Others speculate that inositol hexaphosphate, along with inositol, are metabolized to inositol triphosphates, which are believed to be involved in cell signaling and regulating cell growth, and that this may underlie its possible effects. Chelation by inositol hexaphosphate of ferrous cations could inhibit the Fenton reaction, a reaction which generates reactive oxygen species. Enhancement of natural killer cell activity is offered as still another speculative mechanism.

PHARMACOKINETICS

It is unclear how much inositol hexaphosphate is absorbed in humans following ingestion. Inositol hexaphosphate may, in part, be hydrolyzed to *myo*-inositol. (See *myo*-inositol.)

INDICATIONS AND USAGE

There is preliminary evidence that inositol hexaphosphate may eventually find some use in the treatment of some cancers.

RESEARCH SUMMARY

A few studies performed *in vitro* and in animal models suggest that inositol hexaphosphate inhibits some cancers, specifically epithelial cancers, including breast and colon cancers. It has also significantly inhibited human rhabdomyosarcoma in an animal model. More research is needed to see whether this substance can play a role in the clinical treatment of some cancers. There is some epidemiologic data suggesting that dietary phytate may have chemopreventive activity.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to an inositol hexaphosphate-containing product.

PRECAUTIONS

Supplemental inositol hexaphosphate should be avoided by pregnant women and nursing mothers, due to lack of long-term safety studies.

ADVERSE REACTIONS

No significant adverse effects were noted in one report on the use of a daily dose of 8.8 grams of inositol hexaphosphate taken for several months.

INTERACTIONS

Inositol hexaphosphate may form chelates with divalent cations such as calcium, magnesium, manganese, zinc, copper and iron found in foods, if taken with foods or nutritional supplements containing these elements. It may also interact with food proteins.