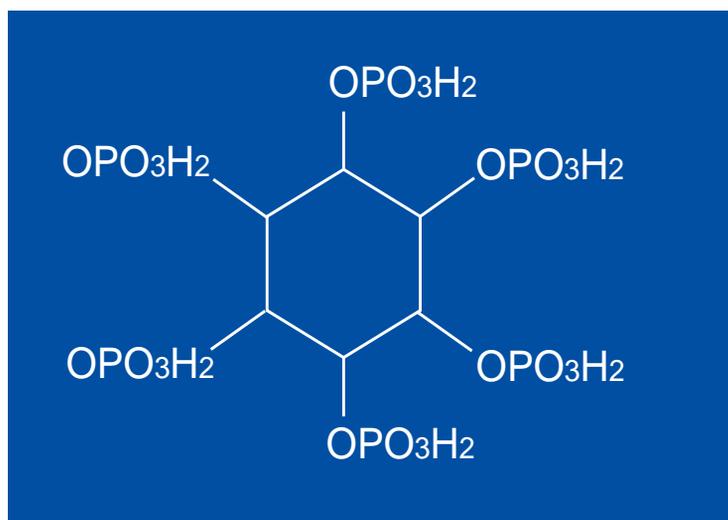


### Chemical Structure of Inositol Hexaphosphate



## Inositol Hexaphosphate

### Introduction

Inositol hexaphosphate (IP6), also known as myo-inositol hexaphosphate and phytic acid, is a naturally occurring compound first identified in 1855. IP6 is found in substantial amounts in whole grains, cereals, legumes, nuts, and seeds, and is the primary energy source for the germinating plant.<sup>1,2</sup> IP6 and its lower phosphorylated forms are also found in most mammalian cells, where they assist

in regulating a variety of important cellular functions.<sup>2</sup> IP6 functions as an antioxidant by chelating divalent cations such as copper and iron, preventing the generation of reactive oxygen species responsible for cell injury and carcinogenesis.<sup>3</sup> Recently, both *in vivo* and *in vitro* studies utilizing IP6 have revealed a significant anticancer activity with a variety of tumor types, possibly via inhibition of tumor cell growth and differentiation.<sup>4</sup> *In vitro* studies with colon, liver, and rhabdomyosarcoma cell lines, and animal models of mammary, colon, intestinal, and liver cancer, as well as rhabdomyosarcoma, have all demonstrated IP6's anticancer properties. Currently, human clinical trials in cancer are lacking. Other properties of IP6 include an anti-platelet aggregating and lipid-lowering effect, suggesting a potential role in cardiovascular disease; inhibition of HIV-1 virus replication; modulation of insulin secretion in pancreatic beta cells; and inhibition of urinary calcium oxalate crystallization, thereby preventing renal stone development.

### Biochemistry and Pharmacokinetics

Inositol phosphates are synthesized from the parent molecule inositol, with daily dietary consumption of inositol estimated at one gram. Once inositol reaches the cells of the intestinal tract, it is phosphorylated to create inositol hexaphosphate,<sup>5,6</sup> and then subsequently dephosphorylated to its lower forms (IP1-5), which play important roles in signal transduction.<sup>4</sup> Independent of the route of administration, IP6 has been found to be absorbed almost instantaneously, transported intracellularly and dephosphorylated into lower inositol phosphates. IP6 can reach targeted tumor tissue as early as one hour post-administration.<sup>7</sup> When incubated with a human mammary cancer cell line, low levels of IP6 were detected as early as one minute post-incubation.<sup>8</sup> Pharmacokinetic studies of IP6 in humans are lacking.

### Mechanisms of Action

The mechanisms of action for IP6 are not completely understood. A recent study supported earlier research that IP6 functions as an antioxidant by chelating divalent cations such as copper and iron, preventing the formation of reactive oxygen species responsible for cell injury and carcinogenesis.<sup>9</sup> The chelation

hypothesis, however, does not completely explain IP6's antineoplastic activity. It is reasonable to conclude that, in addition to its antioxidant role, IP6 probably exerts its action via control of cell division. In a recent study it was shown that IP6 decreased S phase and arrested cells in the G0/G1 phase of the cell cycle. A significant decrease in the expression of proliferation markers indicated IP6 disengaged cells from actively cycling.<sup>10</sup> In addition, IP6 has been shown to enhance NK-cell activity, thereby boosting NK-cell cytotoxicity.<sup>11</sup> Although mechanisms of action pertaining to IP6's anti-platelet aggregating and lipid-lowering effect, its inhibition of HIV-1 replication, and its ability to modulate insulin secretion remain somewhat unclear, it is likely they are a function of IP6's antioxidant properties or its ability to influence a variety of cellular functions. Studies of IP6 and urolithiasis have indicated it inhibits crystallization of calcium oxalate salts in the urine, preventing renal stone development.<sup>12</sup>

## Deficiency States

Deficiencies of IP6 have been associated with an increase in calcium oxalate crystals in the urine and resulting increased risk for kidney stone formation.<sup>12</sup> Due to its antioxidant and antineoplastic properties, IP6 deficiency may also pose an increased risk for disease states mediated by reactive oxygen species, such as cardiovascular disease and cancer.

## Clinical Indications

### Colon Cancer

Epidemiological studies and animal research have suggested an inverse relationship between colon cancer and consumption of high-fiber foods. Among the many components of fiber, inositol hexaphosphate has been studied extensively for its inhibitory effects against colon carcinogenesis. Rat studies have demonstrated IP6 reduces tumor prevalence, frequency, and size in a dose-dependent manner during the initiation and post-initiation stages.<sup>13,14</sup> Another study examining the preventive effects of wheat bran fractions in rat colon cancer showed that removal of both

IP6 and lipids from wheat bran significantly increased colon tumor multiplicity and volume. Removal of IP6 or lipids independent of each other had no significant effect on colon tumor incidence,<sup>15</sup> possibly suggesting the two fractions operate together to inhibit carcinogenesis.

### Breast Cancer

Based on studies of IP6's antineoplastic properties in colon cancer models, animal studies have been conducted to assess its effect on mammary carcinoma. A consistent, reproducible, and significant inhibition of mammary cancer by IP6 has been shown in 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary cancer in rats. A significant reduction was observed in tumor number, multiplicity (number of tumors per tumor-bearing animal), and tumor burden. It was also noted that IP6 protected rats from spontaneous mammary tumors. This study demonstrated IP6 was more effective than a high fiber diet in preventing experimental mammary tumors.<sup>16</sup> Thompson and Zhang also reported a reduction of early markers of experimental mammary carcinogenesis.<sup>17</sup> In another study by Vucenik et al, IP6 and inositol were examined for their effect on DMBA-induced rat mammary tumors. Tumor-bearing animals were given IP6 alone, inositol alone, or IP6 plus inositol, with controls receiving neither substance. Rats treated with IP6 plus inositol showed a 48-percent reduction in tumor multiplicity as well as slight decreases in tumor size and incidence, when compared with control animals. Data from this study suggests IP6 plus inositol may be protective against mammary carcinoma in animals. Additional studies in humans are warranted.<sup>18</sup>

### Hepatocellular Carcinoma

IP6 has demonstrated both *in vivo* and *in vitro* inhibition of the human liver cancer cell line, HepG2. Research conducted by Vucenik et al assessed whether IP6 could inhibit tumorigenicity and suppress or regress growth of HepG2 cells in a transplanted nude mouse model. In mice receiving HepG2 cells pretreated with IP6, no tumor was

found, compared to a 71-percent tumor incidence in mice receiving untreated HepG2 control cells. In the tumor suppression/regression arm of the study, tumors were allowed to reach a diameter of 8-10 mm at which point intra-tumoral injection of IP6 was performed for 12 consecutive days. At autopsy, tumor weight in IP6-treated animals was 86-1180 percent (340-percent average) less than in control mice. This data indicates IP6 inhibits formation of liver cancer and regresses pre-existing human hepatic cancer xenografts.<sup>19</sup>

### **Rhabdomyosarcoma**

Rhabdomyosarcoma (RMS) is a tumor of mesenchymal origin and is the most common soft tissue sarcoma in children. Patients with advanced metastatic RMS frequently do not respond to therapies currently available. *In vitro* and *in vivo* research of IP6's effect on human rhabdomyosarcoma cell line demonstrated IP6 suppressed the growth *in vitro* in a time and dose-dependent manner and also induced cell differentiation. A 50-percent inhibition of cell growth was seen with < 1.0 mM IP6. However, the removal of IP6 from the media after 72 hours of treatment allowed the cancerous cells to recover their growth. In xenografted nude mice IP6 suppressed RMS cell growth *in vivo*. IP6-treated mice produced 25-fold smaller tumors after two weeks of treatment when compared to controls. When the treatment period was extended to five weeks, a 49-fold reduction in tumor size was noted.<sup>20</sup> The results of this research suggest a potential therapeutic role for IP6 in RMS and possibly other mesenchymal neoplasms.

### **Cardiovascular Disease**

#### **Dyslipidemia**

IP6's antioxidant function allows it to form complexes with cations linked to the etiology of hypercholesterolemia. The effect of IP6 was examined in rats fed both standard rodent chow (low in saturated fat) plus monopotassium phytate, and chow plus cholesterol and monopotassium phytate. In the treated groups, IP6 resulted in a 19-percent decrease in total cholesterol in the chow group and a 32-percent decrease in total chole-

sterol in the cholesterol-enriched chow group. The mean triglyceride level decreased also by an average of 65 percent in both groups.<sup>21</sup>

#### **Platelet Aggregation**

Platelet adhesion to endothelial cells and subsequent aggregation are key steps in the development of atherosclerosis. A study of IP6's effect on platelet aggregation was conducted using whole blood obtained from 10 healthy volunteers. Aggregation of activated platelets, incubated with IP6, was significantly inhibited in a dose-dependent manner, suggesting a potential role in reducing cardiovascular disease risk.<sup>22</sup>

#### **HIV**

*In vitro* studies have indicated that IP6 incubated with HIV-1 infected T cells inhibited the replication of HIV-1.<sup>23,24</sup> Although the mechanisms of IP6 action have not yet been determined, the researchers speculate that it acts on HIV-1 early replicative stage since the IP6 was only in actual contact with the cells during the period of viral infection. IP6 was subsequently removed and cells were cultured for five days.<sup>24</sup>

#### **Insulin Secretion**

Research has shown an influx of extracellular calcium is one of the events that drives insulin release.<sup>25</sup> IP6 may be a key element in modulating insulin secretion via its effect on calcium channel activity and the fact that it is the dominant inositol phosphate in insulin-secreting pancreatic beta cells.<sup>26</sup> The mechanism of action is not fully understood but it appears IP6 specifically inhibits serine threonine protein phosphatase activity, which in turn opens intracellular calcium channels, driving insulin release.<sup>25</sup>

#### **Urolithiasis**

Research has shown IP6 significantly inhibits the precipitation of urinary calcium oxalate crystals. Inadequate intake of IP6 in the diet results in a deficiency of urinary IP6 and may pose an increased risk for the development of calcium oxalate kidney stones.<sup>12,27,28</sup>

## Drug/Nutrient Interactions

IP6 strongly binds divalent minerals such as magnesium, iron, calcium, and zinc, and may cause mineral deficiencies if not taken away from meals and mineral supplements. One study demonstrated that phytate-enriched infant formula given to infants younger than four months resulted in a decrease in bioavailability of zinc.<sup>29</sup> The U.S. Department of Agriculture is currently developing first-generation low-phytate hybrid lines of maize, barley, rice, and soybean in an attempt to circumvent mineral depletion by IP6.<sup>30</sup>

## Side Effects and Toxicity

Animal studies have shown IP6 is very safe and without toxic effects, even when administered long term and/or at high doses.<sup>14,31</sup> Regarding toxicity in humans, sodium-IP6 administered to 35 patients at a dose of 8.8 grams per day (in divided doses) for several months resulted in no apparent toxicity.<sup>32</sup>

## Dosage

Dosage information for humans is limited and the optimal IP6 dosage for cancer treatment is yet to be determined. It is typically dosed at two grams and above daily in divided doses. A study in which IP6 was given to patients at risk for kidney stones utilized doses of 8.8 grams daily.<sup>32</sup>

## Warnings and Contraindications

Due to its strong binding affinity for minerals, inositol hexaphosphate should be taken separately from meals, mineral supplements, and multivitamins containing minerals to prevent the potential deficiency that may result.

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