Are there Adverse Effects of Lycopene Exposure?\(^1\)

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EXPANDED ABSTRACT

KEY WORDS: • lycopene • tomatoes • toxicity • safety

Safety studies have been conducted on synthetic lycopene or tomato concentrates. These studies include animal and in vitro studies that have evaluated acute toxicity, subchronic and chronic safety, reproductive effects, genotoxicity, hepatic uptake, and the absorption, distribution, and metabolism of lycopene. Many of these studies were conducted by Roche Vitamins and reported as internal Roche research reports that have been summarized by McClain and Bausch (1). Based on the review of the available toxicology studies, no adverse effects were observed at intake levels up to 3 g/(kg · d) for dietary or formulated lycopene. Formulated lycopene is synthetic, includes antioxidants to prevent lycopene oxidation, and is a common form in which lycopene supplements are marketed. Because of the lack of adverse effect data for lycopene in animals or healthy humans, the Institute of Medicine (IOM)\(^3\) did not set a tolerable upper intake level for lycopene (2). Synthetic lycopene, tomato lycopene extracts, and crystallized lycopene extract are generally recognized as safe (GRAS) for use as an ingredient when added to a variety of foods.

Acute, subchronic, and chronic toxicity studies

Mice were given a single dose of 3 g/kg crystalline (e.g., unformulated) lycopene by various routes of administration. There were no adverse effects when mice were given lycopene orally or intraperitoneally. There was, however, a transient decrease in body tone when lycopene was given by subcutaneous injection (3). When rats were fed 1 g/(kg · d) of crystalline lycopene, there were no adverse clinical signs or histopathology (4). Furthermore, up to 3 g/(kg · d) of formulated lycopene exhibited no effects on body weight, hematology, blood chemistry, ophthalmologic variables, or histology in rats (1,5). When rats were fed varying doses [0 to 616 mg/(kg · d)] of lycopene derived by the fungus *Blakeslea trispora*, there were no adverse effects on clinical or neurological observations, motor activity, consumption, clinical chemistry, or hematology (6). Similarly, when 1 dog was given 100 mg/(kg · d) of crystalline lycopene for 6 mo, no abnormal histological, hematological, or blood chemistry variables were observed (4).

Reproductive studies

Christian and co-workers (7) conducted a study on rats and rabbits in which 0, 0.5, 1.5, or 3 g/(kg · d) of formulated lycopene was given during gestation. There was no effect of lycopene intake on body weight, necropsy findings, fetal development, or skeletal morphology of the offspring. When pregnant rats were given 1 g/(kg · d) of crystalline lycopene for 200 d, there was evidence of pigment accumulation in the liver; however, there were no signs of histopathology. Furthermore, there was no effect on the number of aborted pregnancies or duration of gestation and no evidence of structural malformations (4). Consumption of 1 g/(kg · d) of formulated lycopene during gestation resulted in no signs of maternal toxicity or teratogenic effects in rats (1).

Genotoxicity studies

A series of studies was conducted by Roche Vitamins in which the mutagenicity of crystalline and formulated lycopene was evaluated using the Ames test with several strains of bacteria (1). There was no mutagenic activity for formulated lycopene. The degradation products of crystalline lycopene, as a result of being exposed to light and air, were shown to exhibit some mutagenic activity. Roche Vitamins tested the mutagenicity of formulated lycopene using mouse lymphoma cells and observed no increase in mutant frequency with lycopene (1).

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\(^1\) Presented as part of the conference “Promises and Perils of Lycopene/Tomato Supplementation and Cancer Prevention,” held February 17–18, 2005, in Bethesda, Maryland. This conference was sponsored by the Division of Cancer Prevention (DCP), Division of Cancer Epidemiology and Genetics (DCEG), Center for Cancer Research (CCR), National Cancer Institute, National Institutes of Health (NIH), Department of Health and Human Services (DHHS); Office of Dietary Supplements (ODS), NIH, DHHS; and the Agricultural Research Services (ARS), United States Department of Agriculture (USDA). Guest editors for the supplement publication were Cindy D. Davis, National Cancer Institute, NIH; Johanna Dwyer, Office of Dietary Supplements, NIH; and Beverly A. Clevidence, Agricultural Research Service, USDA.

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\(^3\) Abbreviations used: GRAS, generally recognized as safe; IOM, Institute of Medicine; NOAEL, no-observed-adverse-effect level.

Hepatic uptake studies

A series of studies evaluated the hepatic uptake of lycopene (1). When rats were fed up to 20 mg/(kg · d) of lycopene as either formulated lycopene or tomato concentrate, the highest concentrations were found in the liver. When these rats were later placed on a lycopene-free diet, lycopene concentrations substantially declined, suggesting that the hepatic accumulation of lycopene is reversible.

Absorption and metabolism

Studies have been conducted in rats using [14C]lycopene for evaluating the absorption and metabolism of lycopene (1,8). Only ~7–10% of lycopene was absorbed, with roughly half being excreted in urine and half retained by the body. A review by Boileau and colleagues (9) reported that rats can achieve lycopene tissue concentrations similar to those observed in humans. Therefore, it appears that rats may be an adequate model for understanding the benefits and safety of lycopene in humans.

Adverse effects in humans

There is a dearth of information on the adverse effects of lycopene in humans. Lycopenemia, characterized by an orange discoloration of the skin, has been observed with high intakes of lycopene-containing foods. One case study reported the incidence of lycopenemia in a 61-y-old woman who had consumed ~2 L of tomato juice daily for several years (10). Although there was evidence of lycopene and fatty deposits in the liver, there was an absence of measurable hepatic dysfunction. After 3 wk of consuming a diet free of tomato juice, the orange discoloration faded. Because of the lack of adverse effect data for lycopene in animals or apparently healthy humans, the IOM did not set a tolerable upper intake level for lycopene (2).

Risk and intake assessment

Based on the various safety studies reviewed, no adverse effects were observed at the highest intake level provided, that is, 3 g/(kg · d) of dietary or formulated lycopene. Therefore, a no-observed-adverse-effect level (NOAEL) of 3 g/(kg · d) is assumed. For a 70-kg man, the assumed NOAEL would be equivalent to 210 g/d. The median and 99th percentile of dietary lycopene intake have been estimated to be as high as 5.2 and 123 mg/d, respectively (11), which are substantially lower than the assumed NOAEL.

GRAS

In 2002, the BASF Corporation submitted a notice to the U.S. FDA that synthetic lycopene is GRAS for use as a food ingredient in various food products at levels ranging from 0.5 to 7%. An expert GRAS panel reviewed the lycopene safety and exposure data and concluded that synthetic lycopene is GRAS under the conditions of its intended use. In 2003 the FDA responded to this notice by indicating that it had no questions regarding the notice. In 2004, LycoRed Natural Products Industries submitted a notice to the FDA that 6% tomato lycopene extract, 1.5% tomato extract, and crystallized tomato lycopene extract are GRAS for use as ingredients in a number of food categories. A LycoRed expert GRAS panel concluded that these 3 products were GRAS for their intended uses. In 2005, FDA indicated that it had no questions regarding this notice.

CONCLUSIONS

Although it has been suggested that high tissue concentrations of carotenoids may exhibit pro-oxidant activity under certain circumstances (12), there are no known adverse effects from consuming dietary or formulated lycopene in the general healthy population. Dietary lycopene intake at levels typically consumed in the United States appears to be safe among the general healthy population.

LITERATURE CITED