

SECTION C:

ANALYTICAL DATA*

***Please refer to the electronic file (CD) submitted with this Qualified Health Claim Petition for database information detailing lycopene levels in various foods developed by the U.S. Department of Agriculture/Agricultural Research Service (also available online at <http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>).**

DOCUMENTS INCLUDED IN SECTION C: ANALYTICAL DATA

I. TOMATO CONSUMPTION IN THE UNITED STATES

II. 'SUGGESTED' DAILY INTAKE OF LYCOPENE

III. LYC-O-MATO[®]--TOMATO LYCOPENE

IV. ADDITIONAL LYC-O-MATO[®] INFORMATION

TOMATO CONSUMPTION IN THE UNITED STATES¹

Tomato Intake

According to analyses by USDA's Economic Research Service (ERS), fresh and processed tomato consumption has increased significantly in the United States over the past 20 years, ranking second to potatoes in farm value and vegetable consumption.² According to the ERS 2003 forecast, total per capita tomato consumption totaled 88.7 pounds; of which 18.4 pounds is fresh tomatoes and 70.3 pounds (approximately 79 percent) is processed tomatoes. Of the processed products, tomato sauces have been estimated to account for 35 percent of the total, tomato paste 18 percent, canned whole tomato products 17 percent, tomato juice 15 percent and ketchup, 15 percent.²

Data from 1994-1996 USDA Continuing Survey of Food Intakes by Individuals (CSFII) indicate that mean tomato consumption (including raw plus processed tomatoes) for one day equaled 28 grams.³ ERS data from the same time period indicated that 81.62% of tomato intake was from processed tomatoes. Tomato consumption has decreased slightly since 1994-1996 as shown in the table below.

| Year | Fresh Pounds Per Person | Processed Pounds Per Person | Total Pounds Per Person |
|------------------------------|-------------------------|-----------------------------|-------------------------|
| 1994 | 16.2 | 76.3 | 92.5 |
| 1995 | 16.8 | 74.6 | 91.4 |
| 1996 | 17.4 | 73.1 | 90.5 |
| 2003 (forecast) ⁴ | 18.4 | 70.3 | 88.7 |

When the average ERS estimate of 81.6% for processed tomato intake for the years 1994-1996 is applied to the 1-day intake data from the 1994-1996 CSFII data, an estimate of the mean gram intake of processed tomatoes can be derived. Additionally, intakes can be further subdivided into the processed categories as shown in the table. Since tomato intake in 2003 was forecast to decline from 1996 by approximately 4 percent, the figures shown in the table are slightly higher than current intakes.

| Mean Intake of Tomatoes 1 day, 1994-1996 ^{3,4} | Processed Tomato Intake | Tomato Sauce Intake | Tomato Paste Intake | Canned Tomato Intake | Tomato Juice Intake | Tomato Ketchup Intake |
|---|-------------------------|---------------------|---------------------|----------------------|---------------------|-----------------------|
| 28 g | 22.85 g | 8.0 g | 4.11 g | 3.88 g | 3.43 g | 3.43 g |

Nutrient Contribution of Tomatoes

Fresh and processed tomatoes are an important dietary source of nutrients among U.S. adults. In a study identifying major food sources of 27 nutrients using data from USDA's 1989-91 CSFII, tomatoes ranked in the top 10 food sources of fiber, vitamin A, vitamin C, vitamin E, carotenes, vitamin B-6, potassium, iron, magnesium and copper.⁵ Tomatoes

were in the top 15 food sources for folate, thiamin and niacin. Specific rankings are shown in the next table.

| Nutrient | Rank of Tomatoes | Contribution of Food Group to Nutrient |
|-------------|------------------|--|
| Fiber | 5 | 5.7% |
| Vitamin C | 2 | 9.3% |
| Vitamin E | 5 | 5.8% |
| Vitamin A | 7 | 3.9% |
| Carotenes | 2 | 8% |
| Vitamin B-6 | 7 | 3.4% |
| Potassium | 5 | 5.9% |
| Iron | 8 | 2.6% |
| Magnesium | 9 | 3.1% |
| Copper | 3 | 6.1% |
| Folate | 12 | 2.0% |
| Thiamin | 13 | 2.1% |
| Niacin | 11 | 2.2% |

LYCOPENE IN PRODUCTS¹

| Product | Serving Size ^a | Mean Lycopene Content (mg/100g) | Range of Lycopene Content (mg/100 g) | Lycopene Content (mg/serving) Mean and range, if given |
|--|---|---------------------------------|--------------------------------------|---|
| Ketchup ^b <i>Examples:</i> Heinz Ketchup Heinz Low Sodium Ketchup Heinz Organic Ketchup | 1 tbsp | 17.01 | 16.78 – 17.23 | 2.89; 2.85 – 2.93 |
| Salsa, processed ^c <i>Examples:</i> Old El Paso Salsa Ortega Salsa | 2 tbsp | 9.28 | No Range Given | 3.71 |
| Sauce, pasta, spaghetti/marinara, ready-to-serve ^b <i>Examples:</i> Bell'Orto Marinara Sauce Bell'Orto Spaghetti Sauce Classico Tomato & Basil Escalon Tuscan Tomato & Herb Pasta Sauce | 125 g | 15.99 | No Range Given | 19.99 |
| Sauce, pizza, canned ^{c,d} <i>Examples:</i> Bell'Orto Pizza Sauce Contadina Pizza Sauce Escalon Classic Italian Pizza Sauce | ¼ cup | 12.71 | No Range Given | 7.63 |
| Soup, tomato, canned, condensed, commercial ^b <i>Examples:</i> Campbell's Tomato Soup | 245 g (120 g condensed soup + water) | 10.92 | No Range Given | 13.10 |

^aReference amount

^bU.S. Department of Agriculture/Agricultural Research Service. "USDA-NCC carotenoid database for U.S. foods-1998." *Nutrient Data Laboratory*; <http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>.

^cNguyen, M, and Schwartz, S. "Lycopene stability during food processing." *Proceedings of the Society for Experimental Biology and Medicine* 1998; 218:101-5.

^dClinton, S. "Lycopene: chemistry, biology, and implications for human health and disease." *Nutrition Reviews* 1998; 56:35-51.

| Product | Serving Size^a | Mean Lycopene Content (mg/100g) | Range of Lycopene Content (mg/100 g) | Lycopene Content (mg/serving) Mean and range, if given |
|--|---------------------------------|--|---|---|
| Tomato juice, canned ^b <i>Examples:</i> DelMonte Tomato Juice | 240 mL | 9.32 | 5.0 – 11.60 | 22.37; 12 – 27.84 |
| Tomato products, canned, paste ^b <i>Examples:</i> Bell'Orto Tomato Paste Contadina Tomato Paste Escalon Fancy Tomato Paste Hunts Tomato Paste Morning Star Tomato Paste | 30 g | 29.33 | 5.4 – 55.45 | 8.80; 1.62 – 16.64 |
| Tomato products, canned, puree ^b <i>Examples:</i> Bell'Orto Tomato Puree Escalon Extra Heavy Tomato Puree | 60 g | 16.67 | No Range Given | 10.00 |
| Tomato products, canned, sauce ^b <i>Examples:</i> Bell'Orto Tomato Sauce Escalon Tomato Sauce Hunts Tomato Sauce | 60 g | 15.92 | 7.3 – 17.98 | 9.55; 4.38 – 10.79 |

^aReference amount

^bU.S. Department of Agriculture/Agricultural Research Service. "USDA-NCC carotenoid database for U.S. foods–1998." *Nutrient Data Laboratory*;
<http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>.

| Product | Serving Size^a | Mean Lycopene Content (mg/100g) | Range of Lycopene Content (mg/100 g) | Lycopene Content (mg/serving) Mean and range, if given |
|---|---------------------------------|--|---|---|
| Tomatoes, red ripe, canned, whole, regular pack ^b <i>Examples:</i> Bell'Orto Peeled Rounds Bell'Orto Diced in Juice Bell'Orto Strips in Juice DelMonte Diced Tomatoes Escalon Peeled Chopped Tomatoes Escalon Peeled Chunky Tomatoes Escalon Whole Peeled Pear Tomatoes in Juice with Basil Escalon Organic Diced Tomatoes in Juice Hunts Diced Tomatoes Morning Star Diced Tomatoes | 130 g | 9.71 | 9.27 – 10.15 | 12.62; 12.05 – 13.20 |
| Tomatoes, sun-dried, in oil ^c | 40 g | 46.5 | No Range Given | 18.60 |
| Vegetable juice cocktail, canned ^b <i>Examples:</i> Campbell's V-8 Juice | 240 mL | 9.66 | No Range Given | 23.18 |

^aReference amount

^bU.S. Department of Agriculture/Agricultural Research Service. "USDA-NCC carotenoid database for U.S. foods–1998." *Nutrient Data Laboratory*; <http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>.

^cClinton, S. "Lycopene: chemistry, biology, and implications for human health and disease." *Nutrition Reviews* 1998; 56:35-51.

Other tomato-based products that contain sufficient tomato solids would also be lycopene sources. Examples include tomato-based soups such as vegetable soup and minestrone soup, tomato-based pasta sauces in addition to marinara sauce, chili sauce, seafood cocktail sauce, and variations of canned tomatoes such as crushed tomatoes and ground tomatoes. Lycopene content may be directly obtained from the manufacturing company.

REFERENCES

1. Prepared by the H.J. Heinz Company.
2. Lucier, G, Lin, B, Allshouse, J, and Kantor, L. "Factors affecting tomato consumption in the United States." *Economic Research Service/USDA 2000*; VGS-282:26-32.
3. U.S. Department of Agriculture/Agricultural Research Service. "Data tables: food and nutrient intakes by individuals in the United States, by region, 1994-96." *CSFII/DHKS 1994-96, 1998*;
<http://www.barc.usda.gov/bhnrc/foodsurvey/pdf/Region.pdf>.
4. U.S. Department of Agriculture/Economic Research Service. "Tomatoes." *Briefing Rooms*; <http://www.ers.usda.gov/Briefing/Tomatoes>.
5. Subar, A, Krebs-Smith, S, Cook, A, and Kahle, L. "Dietary sources of nutrients among US adults, 1989 to 1991." *Journal of the American Dietetic Association* 1998; 98:537-47.

'SUGGESTED' DAILY INTAKE OF LYCOPENE

Dr. A. V. Rao
Professor Emeritus
Department of Nutritional Sciences
Faculty of Medicine
University of Toronto

Introduction

There is compelling evidence to suggest a causal relationship between diet and chronic diseases. More recently, 'oxidative stress' has been implicated as an important causative agent of several chronic diseases including cancer, cardiovascular disease, diabetes and osteoporosis. Oxidative stress is induced by the formation of the reactive oxygen species (ROS) through normal metabolic activity and through life style factors including the diet. Being very highly reactive, ROS have the ability to interact with critical cellular components such as lipids, proteins and DNA and cause cellular damage. Oxidation of the cellular components is thought to be an important initial stage in the initiation and progression of cancer and cardiovascular diseases. Antioxidants have the ability to interact with ROS and mitigate their damaging effects. The role of certain enzymes such as superoxide desmutase, glutathione peroxidase and catalase; vitamins such as ascorbic acid, tocopherol and beta carotene; and minerals such as selenium have long been known for their antioxidant properties. Several phytochemicals are now being recognized as having antioxidant properties as well. Among the phytochemicals, the water-soluble polyphenols and the fat-soluble carotenoids are the most prominent. There is considerable interest in lycopene, the carotenoid antioxidant present in tomatoes and processed tomato products, and its role in the prevention of cancer and other chronic diseases.

Lycopene is a straight chain hydrocarbon consisting of 13 double bonds of which 11 are conjugated double bonds. As a result, it is a potent singlet oxygen quencher. Since it lacks the terminal beta ionic rings it does not have the pro-vitamin A activity that beta carotene does. Although lycopene is present in its all-trans isomeric form in tomatoes, it can be converted to several of its cis- isomers upon thermal processing of raw tomatoes (11). Humans and animals lack the ability to synthesize lycopene and therefore it has to be provided through the diet. Although lycopene is present in several fruits and vegetables, its main dietary sources are the tomatoes and tomato products (2, 17). Close to 90% of the daily intake of lycopene comes from tomatoes and processed tomato products. Studies have shown the bioavailability of lycopene to be much greater from processed tomato products than from the raw tomatoes (10). Break-up of the tissue matrix holding the lycopene and its conversion to the cis-isomers are thought to be responsible for more efficient absorption from the processed tomato products. Although initial studies were focused on the biological effects of lycopene alone, recent studies have shown that lycopene acts synergistically with other phytonutrients that are present in the tomatoes. In this respect food sources of lycopene are thought to be superior since they provide a milieu of other beneficial phytonutrients in addition to lycopene.

A study published in 1995 (5) showed that a diet rich in tomatoes, tomato products and lycopene was inversely related to the incidence of prostate cancer. A follow up publication summarized the results of a meta-analysis evaluating 75 studies on the role of lycopene on risk of various cancers (6). The majority of the studies reviews showed significant inverse relationships between the consumption of lycopene and serum levels of lycopene and the risk of various cancers including prostate cancer (5, 6, 7, 9). Since then several other epidemiological and experimental studies have confirmed these observations. The hypothesis emerging from these observations is that the ROS can interact with cellular DNA and cause its oxidation resulting in DNA lesions. These lesions can further develop into cancer cells, proliferate to form tumors, and metastasize. Antioxidants such as lycopene can interact with ROS, prevent oxidation of DNA and reduce the risk of developing cancer. Several animal and human studies have shown that prostate is one of the organs that accumulates lycopene. It may therefore be an important target organ for protection against cancer by lycopene.

Dietary Intakes of Lycopene

Since humans do not synthesize lycopene, it has to be provided through the diet. Estimating the dietary intakes of lycopene by various populations around the world is made difficult due to the variability in the reported levels of lycopene in food sources. However, several reports have appeared in the literature showing average daily intake levels of lycopene. The following table summarizes the reported levels of lycopene intake in different regions of the world (11).

| <u>Country</u> | <u>Average Daily Intake (mg)</u> |
|--------------------------|----------------------------------|
| United States of America | 3.70-16.15 (18-20) |
| Canada | 25.20 |
| Germany | 1.30 |
| United Kingdom | 1.10 |
| Finland | 0.70 |

Other studies have indicated the average intake of lycopene in North America to be 5.3 mg per day. However, 50% of the population was shown to consume 1.86 mg per day or even less in some cases (1, 16).

Although there is a need to make more accurate estimations of lycopene intake by various populations, the general thinking among scientists is that the average intake levels of lycopene in North America are lower than the levels required for its beneficial biological effects. Hence there may be a need to encourage the incorporation of lycopene such as the tomato products as part of a healthy diet and a healthy life style.

Assessment of Lycopene Absorption and In-Vivo Antioxidant Properties

Until recently, nutritionists failed to recognize the importance of lycopene in human health due to its lack of provitamin A activity. As a result, at present, it is not considered as an 'essential' nutrient and as such there is no established Dietary Reference Intake (DRI) levels for lycopene. However, with the recognition of the role of lycopene in human health, there is considerable interest now among nutritionists and other health professionals to make 'suggestions' based on scientific knowledge about its daily intake levels. The main assumption regarding the role of lycopene in the prevention of cancer is that it has to be absorbed from the diet and be present at the site of its action (16). Serum and plasma levels of lycopene have been used extensively to assess the absorption of lycopene from dietary sources and to assess its biological significance (10). Adipose fat levels of lycopene have also been used and are considered a more accurate reflection of lycopene status in the body (11). However, due to the invasive nature of collecting adipose tissue samples, circulatory levels are still considered as standard procedure to assess lycopene absorption. In addition to the levels of lycopene in serum/plasma, measuring the biomarkers of oxidative stress are also used to assess the biological activity of lycopene including its effect on the prevention of prostate cancer (1, 3, 4, 8, 10, 13, 14). The rationale being that in the presence of the antioxidant lycopene, the biomarkers of oxidative stress will be lower. Since oxidative stress is related to the risk of prostate cancer, lower levels of oxidative stress are considered consistent with lower risk of prostate cancer. A few studies have also measured biochemical and pathobiological markers of prostate cancer in patients with cancer after lycopene intervention (9). However, the levels of lycopene used in these studies were based on preliminary studies investigating the absorption and oxidative stress status in healthy and at risk for cancer patients. Dose response studies have not been undertaken.

Lycopene and Prostate Cancer

Prostate cancer is the most common cancer among men and the second leading cause of cancer-related deaths in North American men (5, 7, 15). Recent epidemiological studies have shown a statistically significant association between the consumption the Lycopene-containing foods or the plasma concentrations and reduced risk of prostate cancer (5, 6, 7). The percent reduction in the risk of prostate cancer in the statistically significant studies varied from 35 to 50%. In the 1995 study from Harvard School of Medicine, strongest association between the intake of tomatoes and tomato products and cancers was for prostate, stomach and lung cancers (5). Foods having significant association with reduced risk of prostate cancer were tomato sauce, tomatoes and pizza. A 35% reduction in the risk of prostate cancer was reported with an intake of more than 10 servings per week of the three lycopene-rich foods (5, 7). In a recent dietary survey, 82% of the total lycopene intake by prostate cancer patients and their age-matched controls were from tomatoes and tomato products (15). A dose dependent reduction in the relative risk of prostate cancer was reported from a RR of 1.0 at an intake level of <2.26 mg lycopene to a RR of 0.79 at an intake of >6.46 mg lycopene (5, 7). Similarly the RR of prostate cancer with the intake of tomato-based food products was reduced from a RR of 1.0 at an intake of <1.5 servings per week to a RR of 0.65 at the intake levels of >10 servings per

week (11). The largest and the most comprehensive study on the correlation between prostate cancer and the intake of tomatoes and tomato-based products is the Health Professionals Follow-up Study (5). A 21% reduction in the risk of prostate cancer was reported in this study with intake levels of lycopene of >6.46 mg per day. In the study that investigated the effect of lycopene supplementation on the spread of prostate cancer among patients with the disease, a reduction in the spread of the cancer was reported at much higher levels (9).

Overall, both epidemiological and experimental studies support the conclusion that high intake of Lycopene-containing foods or higher levels of serum/plasma lycopene are inversely related to the risk of prostate cancer. It is therefore prudent to recommend inclusion of foods such as tomatoes and tomato products that are good sources of dietary lycopene in the prevention of prostate cancer and perhaps even in the treatment of the disease.

Suggested Intake Levels of Lycopene in Tomato Products

In a recently reported study, when human subjects refrained from the consumption of lycopene containing foods their serum lycopene levels fell significantly within two weeks (11, 16). This observation was consistent with the fact that humans do not synthesize lycopene and have to be provided with dietary sources to maintain circulatory lycopene levels. Another study was undertaken to investigate the absorption of lycopene in healthy human subjects (11). A total of 19 subjects (male and female) underwent a wash out period during which they refrained from consuming foods that were known sources of lycopene. Following the washout period subjects consumed tomato juice, tomato sauce or lycopene oleoresin capsules for a period of one week in a randomized cross over study design. Subjects underwent a wash out period between the treatments. The lycopene levels varied from 28 mg to 150 mg per day. Lycopene was found to be absorbed equally efficiently from all three sources of lycopene. Increased levels of serum lycopene paralleled significant reductions in lipid, protein and DNA oxidation (11). Based on these studies an intake level of 30-35 mg of lycopene per day was suggested. In a later study, lower levels of lycopene (5, 10 and 20 mg per day) from either tomato ketchup or lycopene oleoresin capsules were studied for their effect on serum lycopene levels and oxidative biomarkers (12). Once again, lycopene was absorbed equally well from both tomato-based sources. At 20 mg of intake the level of lycopene in the serum was not statistically different from 10 mg of intake. Based on the results from this study the previously 'suggested' levels of lycopene intake of 30 – 35 mg could be lowered to 5-7 mg per day. At these levels of intake, a maximum level of serum lycopene and reduction in lipid, protein and DNA oxidation was observed.

Although the suggested level of 5-7 mg of lycopene per day is based on one recent study (12), nevertheless, this range of intake (5-7mg) is consistent with the observation that intake of 6.46 mg of lycopene from tomato products lowered the risk of prostate cancer markedly (5,7). This level of intake is achievable in the recommended diet for healthy eating.

Conclusion

There is compelling scientific evidence to suggest an important role of nutrition in health and disease prevention. Oxidative stress is now recognized as one of the main risk factors for chronic diseases. Antioxidants can play a significant role in mitigating the damaging effects of oxidative stress and lowering the risk of prostate cancer and other chronic diseases. Fruits and vegetables are good sources of natural antioxidants. One such antioxidant is the lycopene present in tomatoes and tomato products. Both epidemiological and experimental studies support the conclusion that increased intake of foods that are good sources of lycopene such as tomatoes and processed tomato products or higher levels of serum/plasma lycopene are inversely related to the risk of prostate cancer. Dietary intake levels of lycopene in North America are reported to be 5.3 mg per day (1,16). The majority of this lycopene comes from processed tomatoes. Raw tomatoes contain predominantly the all-trans lycopene, which is not absorbed as efficiently as that from processed tomatoes.

Fifty percent of the population is reported to consume an average of 1.86 mg of lycopene per day or less (1,16). These data suggest a need to increase the intake levels of dietary lycopene. Lycopene-rich foods such as processed tomato products should be a part of a healthy diet consistent with lower risk of prostate cancer and other chronic diseases. An alternative could be tomato concentrate capsules. Research indicates 5-7 mg of lycopene per day should be the recommended daily intake (RDI).

REFERENCES

1. Agarwal, S, and Rao, A. "Tomato lycopene and its role in human health and chronic diseases." *Canadian Medical Association Journal* 2000; 163:739-44.
2. Agarwal, A, Shen, H, Agarwal, S, and Rao, A. "Lycopene content of tomato products: its stability, bioavailability and *in vivo* antioxidant properties." *Journal of Medicinal Food* 2001; 4:9-15.
3. Agarwal, S, and Rao, A. "Carotenoids and chronic diseases." *Drug Metabolism and Drug Interactions* 2000; 17:189-210.
4. Agarwal, S, and Rao, A. "Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study." *Lipids* 1998; 33:981-4.
5. Giovannucci, E, Ascherio, A, Rimm, E, Stampfer, M, Colditz, G, and Willett, W. "Intake of carotenoids and retinol in relation to risk of prostate cancer." *Journal of the National Cancer Institute* 1995; 87:1767-76.
6. Giovannucci, E. "Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature." *Journal of the National Cancer Institute* 1999; 91:317-31.
7. Gann, P, Ma, J, Giovannucci, E, Willett, W, Sacks, F, Hennekens, C, and Stampfer, M. "Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis." *Cancer Research* 1999; 59:1225-30.
8. Jain, C, Agarwal, S, and Rao, A. "The effect of dietary lycopene on bioavailability, tissue distribution, *in vivo* antioxidant properties and colonic preneoplasia in rats." *Nutrition Research* 1999; 19:1383-91.
9. Kucuk, O, Sarkar, F, Sakr, W, Djuric, Z, Pollak, M, Khachik, F, Li, Y, Banerjee, M, Grignon, D, Bertram, J, Crissman, J, Pontes, E, and Wood, D. "Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy." *Cancer Epidemiology, Biomarkers and Prevention* 2001; 10:861-8.
10. Rao, A, and Agarwal, S. "Role of antioxidant lycopene in cancer and heart disease." *Journal of the American College of Nutrition* 2000; 19:563-9.
11. Rao, A. "Lycopene, tomatoes and health: new perspectives 2000." In Lycopene and the Prevention of Chronic Diseases, (Rao, A, and Heber, D, eds.), Caledonian Science Press, Scotland, UK (2002), pp. 19-28.
12. Rao, A, and Shen, H. "Effect of low dose lycopene intake on lycopene bioavailability and oxidative stress." *Nutrition Research* 2002; 22:1125-31.

13. Rao, L, Guns, E, and Rao, A. "Lycopene: its role in human health and disease." *Agro Food Industry Hi-Tech* 2003; 14:25-30.
14. Rao, A, and Agarwal, S. "Bioavailability and *in vivo* antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer." *Nutrition and Cancer* 1998; 31:199-203.
15. Rao, A, Fleshner, N, and Agarwal, S. "Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: a case-control study." *Nutrition and Cancer* 1999; 33:159-64.
16. Rao, A, and Agarwal, S. "Role of lycopene as antioxidant carotenoid in the prevention of chronic diseases: a review." *Nutrition Research* 1999; 19:305-23.
17. Rao, A, Wasecm, Z, and Agarwal, S. "Lycopene content of tomatoes and tomato products and their contribution to dietary lycopene." *Food Research International* 1998; 31:737-41.
18. U.S. Department of Agriculture/Agricultural Research Service. "USDA-NCC carotenoid database for U.S. foods-1998." *Nutrient Data Laboratory*; <http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html>.
19. Block, G, Coyle, L, Hartman, A, and Scoppa, S. "Revision of dietary analysis software for the Health Habits and History Questionnaire." *American Journal of Epidemiology* 1994; 139:1190-6.
20. U.S. Department of Agriculture/Agricultural Research Service. "CSFII 1994-96, 1998." *Food Surveys Research Group*; <http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm>.
21. Forman, M, Lanza, E, Yong, L, Holden, J, Graubard, B, Beecher, G, Meltiz, M, Brown, E, and Smith, J. "The correlation between two dietary assessments of carotenoid intake and plasma carotenoid concentrations: application of a carotenoid food-composition database." *American Journal of Clinical Nutrition* 1993; 58:519-24.

LYC-O-MATO®-TOMATO LYCOPENE

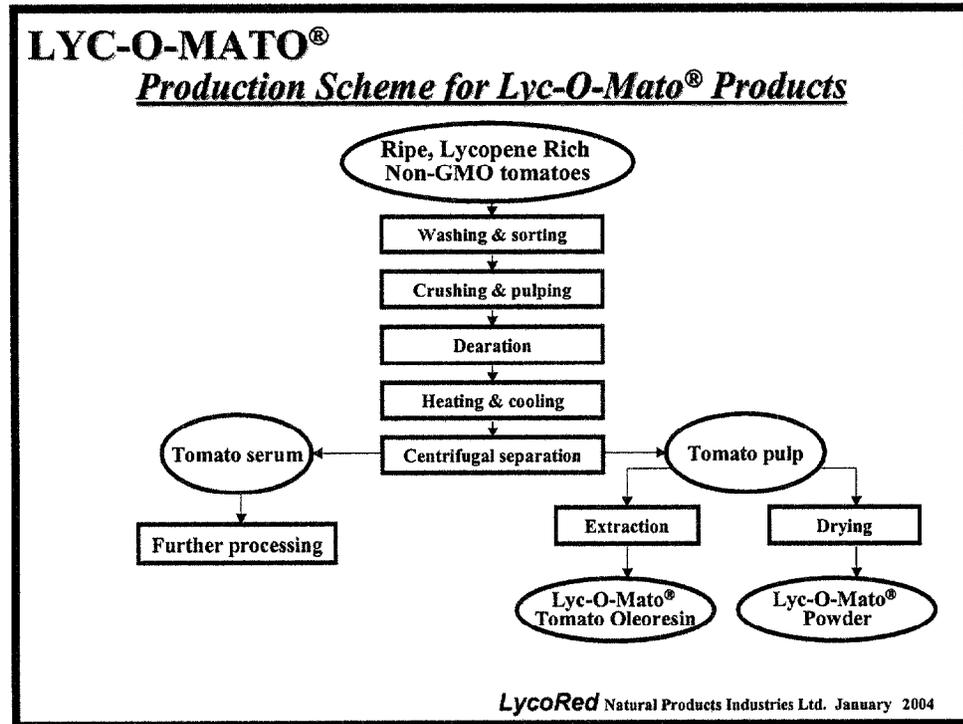
The LycoRed process uses conventional physical unit operations to separate the ripe tomatoes into serum and pulp. The pulp is then extracted in a similar manner as various oils are being produced from their corresponding plant sources.

Since the tomato is a seasonal (summer) crop, the process is conducted in two stages. The pulp is prepared in the season, kept frozen and under vacuum, and used throughout the year to extract the tomato oleoresin

In the processing plant the tomatoes are thoroughly washed and processed into tomato pulp. The tomato pulp separated from the serum is packed under vacuum and kept frozen (-18°C) until it is extracted in a specially designed modern facility. The proprietary (US Patent No. 5,837,311) process uses conventional unit operations approved for the food industry. There is no chemical intervention in the process.

Throughout the production special care is taken to protect the lycopene from high temperatures and from prolonged contact with the air. This assures that lycopene is protected from isomerization and degradation. Strict quality control accompanies the various stages of production, from cultivating the tomatoes in the field to the standardizing of the oleoresin for production of various formulations. The processing is ISO-9002 certified and GMP approved. Each production batch is continuously tracked so that it can be traced back all the way to a particular lot of tomatoes in the field.

PRODUCTION SCHEME FOR LYC-O-MATO® PRODUCTS



The tomato pulp produced in the process can either be dried to Lyc-O-Mato® Powder or extracted to produce the Lyc-O-Mato® oleoresin.

The oleoresin consists of tomato lipids. It contains a high concentration of lycopene, partially dissolved and mostly dispersed in tomato oil, as well as several other important phytonutrients. The ratio between the lipid phytonutrients that is found in the ripe tomato is preserved in the oleoresin

CONTENT OF PHYTONUTRIENTS IN THE TOMATO AND IN LYC-O-MATO[®] EXTRACT: TYPICAL ANALYSIS

| Phytonutrient | Content in ripe tomato (ppm) | Ratio of total Lycopene in ripe tomato | Content in Lyc-O-Mato [®] extract (%) | Ratio of total Lycopene in Lyc-O-Mato [®] |
|-----------------------|------------------------------|--|--|--|
| Lycopene Trans isomer | 147.0 | 92.0 | 5.5 | 91 |
| Lycopene Cis isomer | 12.8 | 8.0 | 1.0 | 8 |
| Total Lycopene | 160.0 | 100.0 | 6.0 | 100 |
| Phytoene | 16.0 | 10.0 | 0.6 | 10 |
| Phytofluene | 14.5 | 9.1 | 0.54 | 9 |
| Vitamin E | 55.0 | 34.5 | 2.0 | 33 |

The oleoresin is standardized to the desired lycopene content by mixing lots of different concentrations and is used in various formulations under the brand name of Lyc-O-Mato[®]. These formulations are used as a source of lycopene in functional foods and in dietary supplements.

Lyc-O-Mato[®] contains other important phytonutrients as well, such as phytoene, phytofluene, beta-carotene, tocopherols and phytosterols. The synergy of these phytonutrients enhances Lyc-O-Mato[®] biological activity.

Scientists that have researched the beneficial effect on health of tomato products, are convinced that it is the synergism between lycopene and other tomato phytonutrients that enhances its ability to curb degenerative diseases. The natural composition of tomato phytonutrients is preserved in the oleoresin. This effect and high lycopene bioavailability was demonstrated in several clinical studies that were conducted with Lyc-O-Mato[®] Oleoresin. Thus Dr. Omer Kucuk⁽¹⁾ conducted a clinical research with prostate cancer patients, a blind, placebo-controlled study was done by Dr. Esther Paran⁽²⁾, evaluating the effect of Lyc-O-Mato[®], a natural tomato extract on 35 mildly hypertensive patients. Dr. Aviram's^(3,4) researched the effects of Lyc-O-Mato[®] Oleoresin on the prevention of LDL oxidation and in vitro work done by Drs. Sharoni and Levi⁽⁵⁾, demonstrated the effective synergy between the tomato phytonutrients in the tomato oleoresin on reducing the proliferation of prostate and breast cancer cells. The Lyc-O-Mato[®] oleoresin was shown to prevent DNA⁽⁶⁾ damage and to protect human skin from solar radiation⁽⁷⁾.

REFERENCES

1. Kucuk, O, Sarkar, F, Sakr, W, Djuric, Z, Pollak, M, Khachik, F, Li, Y, Banerjee, M, Grignon, D, Bertram, J, Crissman, J, Pontes, E, and Wood, D. "Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy." *Cancer Epidemiology, Biomarkers and Prevention* 2001; 10:861-8.
2. Paran, E, and Engelhard, Y. "Effect of tomato's lycopene on blood pressure, serum lipoproteins, plasma homocysteine and oxidative stress markers in grade I hypertensive patients." *American Journal of Hypertension* 2001; 14:141A.
3. Fuhrman, B, Ben-Yaish, L, Attias, J, Hayek, T, and Aviram, M. "Tomato lycopene and β -carotene inhibit low density lipoprotein oxidation and this effect depends on the lipoprotein vitamin E content." *Nutrition, Metabolism, and Cardiovascular Diseases* 1997; 7:433-43.
4. Fuhrman, B, Volkova, N, Rosenblat, M, and Aviram, M. "Lycopene synergistically inhibits LDL oxidation in combination with vitamin E, glabridin, rosmarinic acid, carnosic acid, or garlic." *Antioxidants and Redox Signalling* 2000; 2:491-506.
5. Sharoni, Y, Agemy, L, Giat, Y, Kirilov, E, Danilenko, M, and Levy, J. "Lycopene and astaxanthin inhibit human prostate cancer cell proliferation induced by androgens." *American Association for Cancer Research; Frontiers in Cancer Prevention Research Conference*; October 14-18, 2002.
6. Rao, A, and Agarwal, S. "Bioavailability and *in vivo* antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer." *Nutrition and Cancer* 1998; 31:199-203.
7. Olivier, A, Wilhelm, S, Helmut, S, Hagen, T, and Ulrike, H. "Supplementation of lycopene-rich tomato extract increases lycopene and its precursors' levels in human serum and reduces UV light-induced erythema." *Submitted for publication.*

DESCRIPTION OF LYC-O-MATO® PRODUCTS

Both Lyc-O-Mato® Oleoresin and Lyc-O-Mato® Powder are produced by LycoRed Natural Products Industries, Ltd., from tomato pulp centrifugally separated from ripe tomatoes. Both products are free from any additives.

Lyc-O-Mato® Oleoresin

Lyc-O-Mato® Oleoresin is an ethyl acetate extract of tomato pulp that contains 5%-15% lycopene as well as other tomato phytonutrients dispersed in tomato oil. The gentle production process prevents oxidation and assures that the tomato components are preserved in their natural state. Lyc-O-Mato® Oleoresin is self-affirmed GRAS, and an FDA response is pending on a color additive petition (CAP) that was filed in 2000. Lyc-O-Mato® Oleoresin can be used in food products and in dietary supplements.

Lyc-O-Mato® Powder

Lyc-O-Mato® Powder production begins with the same tomato pulp that is extracted to produce the Lyc-O-Mato® Oleoresin. However, production of Lyc-O-Mato® Powder involves careful dehydration, rather than extraction, of the tomato pulp. The gentle process employed protects the sensitive phytonutrients from oxidation and assures that the Lyc-O-Mato® Powder has a similar composition profile of phytonutrients to that of the tomato. Lyc-O-Mato® Powder contains a minimum of 0.8% lycopene, up to a maximum 2% lycopene.

Lyc-O-Mato® Beadlets

Lyc-O-Mato Beadlets consist of microencapsulated Lyc-O-Mato® Oleoresin in a gelatine or vegetable gum matrix. The beadlets are used as a source of lycopene and tomato phytonutrients in dietary supplements.