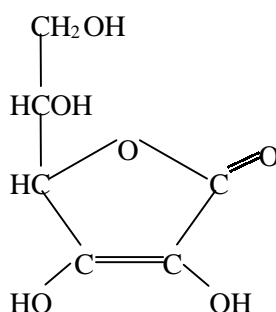


The production of vitamin C

Chemical structure

1. The official chemical designation for vitamin C is ascorbic acid.¹ It was discovered in 1912 and first isolated in lemons in 1933. Its chemical structure, which was determined in 1933, is shown below.



Production

2. Vitamin C has been produced commercially by extraction from plants, by chemical synthesis, by fermentation and by mixed fermentation/chemical synthesis methods. (Fermentation is a chemical reaction in which a micro-organism or enzyme causes an organic compound to split into simpler substances.) The manufacture of vitamin C is now carried out in two ways.² Figure 1 shows the main steps in the two processes.

3. In the first step of both the traditional Reichstein process and the newer two-stage fermentation process, sorbitol is oxidized into sorbose by fermentation. All producers use the same micro-organism for this fermentation. (Sorbitol itself is made by reducing glucose at high temperature.) Neither the Reichstein process, nor the two-stage fermentation process, involves the use of genetically modified organisms (GMOs).

Reichstein process

4. The Reichstein process is a mixed fermentation/chemical synthesis method. It was first used in 1933 and is still employed by Roche, BASF and Takeda. In it, sorbose is transformed into di-acetone-ketogulonic acid (DAKS) in a two-stage chemical process. The first step involves a reaction with acetone. This produces di-acetone sorbose, which is then oxidized using chlorine and sodium hydroxide to produce DAKS.

5. In the next step, DAKS is dissolved in a mix of organic solvents and its structure is rearranged to form vitamin C, using an acid catalyst. (This stage of the process is similar in the two-stage fermentation process.) In the last production step, the crude vitamin C is purified by recrystallization. (This step is identical for both processes.)

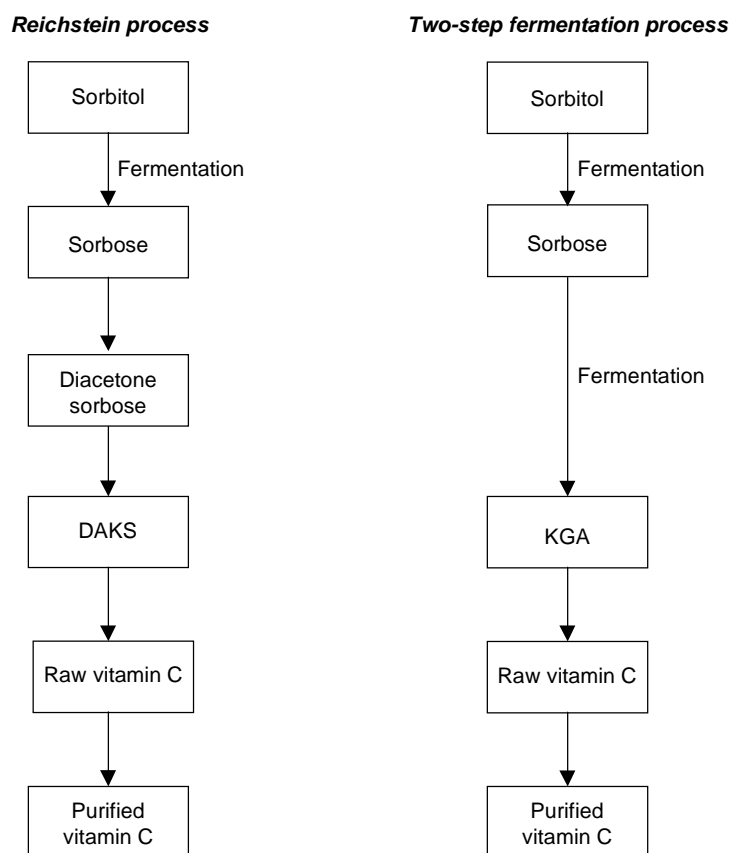
6. Many technical and chemical modifications have been made to the Reichstein process to optimize and shorten the various reaction routes. Consequently, each step now has a yield of over 90 per cent. The overall yield of vitamin C from glucose is about 60 per cent.

¹Commission on Biochemical Nomenclature, 1965.

²For a full description of the processes used see *Ullmann's Encyclopedia of Industrial Chemistry*, VCH Verlagsgesellschaft mbH, 1996.

FIGURE 1

Methods of producing vitamin C



Source: BASF.

7. Various stages of the Reichstein process use considerable quantities of organic and inorganic solvents and reagents. These include acetone, sulphuric acid and sodium hydroxide. Although some of these compounds can be recycled, stringent environmental control is required, resulting in significant waste disposal costs.

Two-stage fermentation process

8. The newer of the two main production processes was developed in China and is used by all Chinese producers. The use of the process has also been licensed to a number of Western manufacturers, including Roche and a joint venture involving BASF and Merck. It has lower fixed and capital costs, resulting in an overall production cost saving of about a third compared with the Reichstein method.

9. In the two-stage fermentation process, a second fermentation step replaces the chemical reactions used to produce DAKS in the Reichstein method. This fermentation results in a different intermediate product, KGA. All producers use the same micro-organism.

10. Two chemical steps similar to the final stages of the Reichstein process then complete the synthesis of vitamin C.

11. Compared with the Reichstein process, the two-stage fermentation process makes less use of toxic solvents and reagents. There is, therefore, a reduction in the cost of processing waste products.

Research into new processes

12. Many patents for the production of vitamin C by different routes have been published. There have been two recent foci of research and development work:

- (a) The first has centred on the development of fermentation methods to transform glucose into KGA, either directly or via sorbitol, sorbose or diketogluconic acid. For example, a joint venture in the USA involving Genencor International, Eastman, Electrosynthesis Company Inc, MicroGenomics Inc and Argonne National Laboratory is seeking to develop a way to manufacture KGA directly from glucose by fermentation (see paragraph 34).
- (b) The second chief area of research has concerned the direct conversion of glucose into vitamin C by fermentation using mutant micro-algae.

Economies of scale

13. As the scale of the plant increases for both the Reichstein process and the two-stage fermentation process, many costs do not rise in proportion. This particularly applies to capital costs, labour costs and energy costs. Larger manufacturers are often also able to negotiate lower raw material costs. These factors give Roche an advantage as its plants are significantly larger than those of other producers. This largely offsets the cost penalty Roche experiences from using the less efficient Reichstein process.

Forms of vitamin C produced

14. Many raw vitamins can be unstable if affected by temperature, light, acidity or alkalinity. To prevent degradation in use, these vitamins may be combined with other products or, alternatively, various chemical derivatives of the vitamins may be produced.

15. Producers market vitamin C in various forms. These include powder and granular forms, different purity levels, and chemical derivatives such as sodium ascorbate and calcium ascorbate. BASF said that sodium ascorbate was preferred as an antioxidant as it would not discolour meat; in other respects it was almost identical in its biochemical properties to ascorbic acid. Calcium ascorbate is also commonly produced for use as a combined source of calcium and vitamin C in supplements.

16. BASF's range of vitamin C products includes ascorbic acid in three particle sizes, sodium ascorbate, and calcium ascorbyl-monophosphate, a product for the feed industry designed to resist severe heat and pressure treatments. It does not produce a DC grade of vitamin C for use in tablets.

17. We were also told about some other minor speciality vitamin C products. These included stay-C, a low-solubility product made by Roche, which is suitable for use in fish feeds. Roche said that BASF had an equivalent product for the fish farming industry, but Takeda did not.

Main manufacturers of vitamin C

18. Table 1 summarizes the production methods used by the manufacturers.

19. BASF estimated the producers' comparative cash operating costs for vitamin C before the merger. Figure 2 summarizes our analysis of the cost ranking that results from combining this with our estimates of plant capacities. No allowance was made for depreciation or any return on capital. BASF's data clearly demonstrate the wide range of manufacturers' cash production costs. No cost estimates were made for Merck or ADM.

TABLE 1 Production methods used by vitamin C manufacturers

<i>Producer</i>	<i>Process</i>	<i>Capacities tonnes per year</i>	<i>Main raw material</i>	<i>Comments</i>
BASF existing	Reichstein/final steps of two-stage fermentation	(∞)	Sorbitol	KGA is transferred from joint venture fermentation plant at Krefeld. To be replaced.
(<i>Details omitted. See note on page iv.</i>)
Takeda	Reichstein	(∞)	Sorbitol	Two plants to be replaced by new BASF plant.
Roche	Reichstein	(∞)	Sorbitol	Two plants. Economies of scale. Highly efficient from long experience of Reichstein process but lacks advantages of two-stage fermentation process.
Chinese producers	Two-stage fermentation	43,000*	Sorbitol	Long experience of two-stage fermentation process. Mix of high- and low-scale plants. Low input costs.
Merck	Final steps of two-stage fermentation	(∞)	Sorbitol	KGA is transferred from joint venture fermentation plant at Krefeld. (∞)
ADM (to start in 2001)	Two-stage fermentation	(∞)	Sorbitol	New plant. Advantageous source of raw material. Fermentation experience. Little experience of chemistry.

Source: BASF and other producers.

*Estimated total capacity at five production sites (see paragraph 28).

FIGURE 2

Ranking of vitamin C production costs against capacity before merger

Details omitted. See note on page iv.

20. Figure 3 shows the corresponding estimates of comparative cash operating costs for vitamin C after the merger and BASF's planned investment. It demonstrates a substantial improvement in BASF's cost competitiveness before allowing for depreciation and a return on investment. No cost estimates were made for Merck, ADM or any new market entrants.

FIGURE 3

Ranking of vitamin C production costs against capacity after merger and investment

Details omitted. See note on page iv.

BASF and Takeda

21. Following the merger, BASF now sources its sales of vitamin C from its plant at Grenaa in Denmark (capacity [] tonnes a year) and from the former Takeda plants at Wilmington in the USA ([] tonnes a year) and Hikari in Japan ([] tonnes a year). We were told that production from these plants, all of which use the Reichstein process, was not cost competitive.

22. KGA is now produced by fermentation by a joint venture of Cerestar Deutschland GmbH, Merck and BASF (KGS-Gesellschaft) at Krefeld in Germany. The plant has a capacity of [] tonnes a year and its output is processed into vitamin C by BASF (using the final processing stages of its plant at Grenaa) and by Merck at Darmstadt. This enables BASF to achieve some of the operating cost savings associated with adopting the two-stage fermentation process.

23. [

Details omitted. See note on page iv.

]

24. In 2000, BASF spent about £3 million on research and development to improve its vitamin C processes; it plans to spend approximately the same amount in the current year. BASF's joint venture with Merck and Cerestar is also carrying out further development work on the two-stage fermentation process licensed from the Chinese.

Roche

25. Roche began producing vitamin C in the 1930s and was the only manufacturer until the 1960s. Although it licensed the two-stage fermentation process from China in the 1980s, Roche never applied the technology commercially. It still uses the higher-cost Reichstein process at its plants at Dalry, in Scotland, and Belvedere, in the USA. However, these plants, which each have a capacity of over [] tonnes a year, benefit from both significant economies of scale and Roche's long experience of optimizing the Reichstein process (see paragraph 4). Roche is currently upgrading its facilities at Dalry further by adding a plant based on the two-stage fermentation process.

Merck

26. Merck's plant at Darmstadt, in Germany, has a capacity of [] tonnes a year. As Merck is a party to the joint venture (including BASF) that produces KGA at Krefeld in Germany (see paragraph 22), it has access to a proportion of the output, which it converts into vitamin C at Darmstadt. [

Details omitted. See note on page iv.

]

Chinese producers

27. A Chinese research team developed the two-stage fermentation process for vitamin C, which is used by all Chinese producers (see Appendix 4.4). Although about 28 plants were built to exploit it in the mid-1980s and early 1990s, many of them stopped producing after prices fell in the late 1990s. Some of these plants could possibly be brought into operation if prices were to increase.

28. As we have only been able to obtain limited information from Chinese producers, we are largely reliant on information supplied by the British Embassy in Beijing, BASF, Roche and AMC and on published sources. Only about five producers now contribute significantly to Chinese exports. Our sources of information produced capacity estimates in the following ranges:

	<i>tonnes per year</i>
North East General Pharmaceutical Co Ltd	11,000–15,000
Jiangsu Jiangshan Pharmaceutical Co Ltd	10,000–11,000
Shijiazhuang Welcome (Weierkang) Pharmaceutical Co Ltd	4,000–13,000
Shijiazhuang No 1 (Weishang) Pharmaceutical Factory	8,000–10,000
Shanghai Sunve (Sanwei) Pharmaceutical Factory	2,000

29. BASF, Roche and many published sources believe that Chinese producers' costs are significantly lower than the production costs of manufacturers elsewhere in the world. BASF told us that this cost advantage arose from using the most efficient production process, having lower labour and investment costs and having to meet less demanding environmental standards. Chinese producers had been able to negotiate low-cost finance from their government; it was therefore relatively easy for them to build a new plant or expand capacity. These advantages were, however, offset by some Chinese plants being too small to realize most of the economies of scale.

30. Many researchers in Chinese universities are working on improved fermentation methods for producing vitamin C that have yet to move from laboratory to industrial scale. Other university scientists are assisting Chinese producers to improve their production technologies or improve their strains.

Archer-Daniels-Midland Company

31. ADM is already producing KGA and intends to enter the vitamin C market in the third or fourth quarter of 2001 after building a plant with a capacity of [] tonnes a year at Decatur, in the USA. It aims to compensate for the comparatively low capacity level by using an advantageous captive source of glucose as its raw material. This glucose is a by-product of its corn-processing activities. ADM has licensed the technology for the chemical stages of the process from Aventis. BASF told us that it considered that ADM's long experience of fermentation would be an asset, although this would be offset by its lack of experience of the chemical stages in the process.

Possible market entry

32. The principal barriers to entry are capital investment, intellectual property rights and operational experience. The cost of entering the market depends on the country in which a new plant is established. BASF told us that it did not believe that a Western plant producing less than 10,000 tonnes a year would be viable in today's market, unless it had particular cost advantages. BASF estimated the capital cost of a two-stage fermentation plant with an annual capacity of 10,000 tonnes to be between €[] million and €[] million (between £[] million and £[] million) for a site in Germany. A larger plant would benefit from economies of scale. In countries with low labour costs, the capital cost would be significantly lower.

33. Research and development programmes generate significant intellectual property rights for established producers. Several stages of vitamin C production are protected by patents, including methods for the esterification of KGA and for the acid-catalysed rearrangement of KGA, its ester or DAKS into vitamin C. In some cases, these patents could be circumvented by modifications to the production process. BASF told us that producers using the two-stage fermentation process needed a licence from a Chinese research institute.

34. In the USA, Genetech has been studying a one-step fermentation method with some promise since 1989. BASF told us that it thought that the conversion yield was, however, too low for commercial production at present. A joint venture involving Eastman and Genencor International hopes to enter the market late in 2003 or early in 2004 with a new process currently under development (see paragraph 12).

35. Established producers gain significant know-how from experience of operating their plants. New plants tend to take a long time to reach full output. BASF told us that a combination of experience and R&D had enabled it both to increase its plants' capacities steadily and to reduce their production costs.