SYNTHETIC ASTAXANTHIN. THE ROUTE OF A CAROTENOID
FROM RESEARCH TO COMMERCIALISATION

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INTRODUCTION

The presently witnessed industrial demand for carotenoids can be mainly attributed to their extraordinary properties as colouring agents and supplements for food and feed. No longer is the importance of colour as an indication of the quality of foodstuffs being ignored.

This change in consumer values is putting pressure on the manufacturers to produce food and feed which does not show the depletion of the natural carotenoids from oxidation as occurs during processing and storage. Thus there is a genuine need to supplement food and feed with nature-identical carotenoids in order to restore them to their original and natural colouring levels.

This necessity is again augmented by the fact that many of the artificial synthetic food dyestuffs being used today may cause allergic reactions in humans, and recently some of them have been banned because of carcinogenic properties. The question of colouring agents in relation to health is being increasingly asked, and it is considered especially beneficial if the coloring agent is linked to a health supporting function. The newly discovered physiological functions of the carotenoids, such as the improvement of fertility in cattle or the probable cancer-preventing activities in humans, will provide additional reasons for demanding the use of carotenoids in food and feed colouring.

The carotenoids can be produced by large scale production means, and this either by extraction from biological organisms or else by chemical synthesis.

Extracts of parts of higher plants have been used for a long time. Well known examples are the bixin-containing seeds of the annatto tree or the capsanthin- and capsorubin-containing oleoresin of paprika fruits for use in food, and the zeaxanthin and lutein-containing marigold petals for poultry feed. A new trend, initiated in the 1970s in Israel and Australia, is the growth of microalgae, e.g. the β-carotene containing Dunaliella, to be used as a whole organism or extracted as a source of carotenoids. The other possibility is to produce carotenoids by total synthesis; microbiological steps may be included in some such processes. The main advantage of synthetic carotenoids is their defined degree of purity, with regard to other carotenoids, pesticides etc., their stability in formulated form and the consistent quality.
Today, six synthetic carotenoids are available on the market:

**Table 1. Commercially Available Carotenoids**

<table>
<thead>
<tr>
<th>Carotenoid</th>
<th>Year of Commercialization</th>
<th>Use</th>
<th>Producers</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-carotene</td>
<td>1956</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Canthaxanthin</td>
<td>1962</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8'-Apo-β-caroten-8'-al</td>
<td>1962</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ethyl 8'-apo-β-caroten-8'-oate</td>
<td>1962</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(3RS,3'RS)-Astaxanthin</td>
<td>1984</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Citranaxanthin</td>
<td>1969</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

In reviewing Roche's activities in the carotenoid field, following guiding ideas can be noted:

- Preference is given to carotenoids occurring naturally in feed or food.

- A limited number of carotenoids with distinct colours are produced, intermediate colour hues are achieved by mixing.

- Considerable efforts are devoted to the elucidation of physiological function and metabolism of carotenoids in humans and animals.

Astaxanthin has been introduced as a sales product for the fish feed industry. The worldwide breeding of salmon by farming methods has increased from nearly zero at the beginning of the 1970s to ca. 100,000 tons in 1987. This amount is expected to double within the next few years. Similar growth rates are expected in the farming of prawns and shrimps. Both the fish and crayfish contain astaxanthin as the main pigment in the wild. The characteristic pink colour of wild salmon cannot be achieved under farming conditions without the addition of a pigment to the diet. Since astaxanthin was not available in sufficient amounts at Roche at the beginning of the 1970s, feeding trials on salmon and trout were performed with available carotenoids which could conceivably be precursors of astaxanthin: astacene and its dipalmitate, canthaxanthin, crustaxanthin, isozeaxanthindiacetate.

Of these carotenoids, only canthaxanthin was deposited in salmon and trout providing a pinkish hue of the flesh.

In the 1960s, Roche scientists had shown that canthaxanthin was present in wild brown trout and in the zooplankton *Daphnia*¹. The registration of canthaxanthin as a fish feed additive was achieved at the end of the 1970s. But astaxanthin, the main carotenoid in the flesh of wild salmon, remained the target compound for a commercial fish feed additive.

Simultaneously, attempts were started up to achieve the isolation, partial synthesis and then total synthesis of astaxanthin.

**NATURAL OCCURRENCE**

Frequently, astaxanthin occurs in nature in the form of a carotenoid protein complex, which may differ widely in colour from yellow to red, blue, green, brown etc. In the carotenolipo(glyco)proteins, astaxanthin is