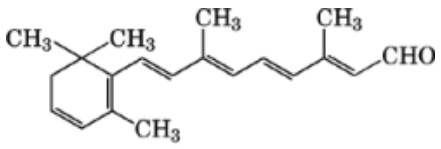
Kirk-Othmer Encyclopedia of Chemical Technology.

VITAMIN A

The curative role of the juice of cooked liver extracts in the treatment of night blindness was first recognized and practiced by the Egyptians in ancient times (1). Several millenniums later, in the early part of the twentieth century, many groups identified a lipid-soluble factor found in milk, butter, and egg yolks which was therapeutic for this condition. In 1913, McCollum and Davis coined the term fat-soluble A and subsequently, ascribed the growth-promoting effects of liver extracts to this material (2, 3). Later, Osborne and Mendel found that cod liver oil contained an ingredient that was essential for growth promotion in rats (4).

The structure of vitamin A [11103-57-4] and some of the important derivatives are shown in Figure 1. The parent structure is all-*trans*-retinol [68-26-8] and its IUPAC name is (all-*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol 1. The numbering system for vitamin A derivatives parallels the system used for the carotenoids. In older literature, vitamin A compounds are named as derivatives of trimethyl cyclohexene and the side chain is named as a substituent. For retinoic acid derivatives, the carboxyl group is denoted as C-1 and the trimethyl cyclohexane ring as a substituent on C-9. The structures of vitamin A and β-carotene were elucidated by Karrer in 1930 and several derivatives of the vitamin were prepared by this group (5, 6). In 1935, Wald isolated a substance found in the visual pigments of the eye and was able to show that this material was identical with Karrer's retinaldehyde [116-31-4] 1 (7).

Vitamin A_2 [79-80-1] **(6)** is structurally similar to vitamin A_1 [68-26-8] and is also found in fish oils. This compound is important biologically for fish and other lower animals. Interestingly, tadpoles require vitamin A_2 but after metamorphosis require vitamin A_1 (8).

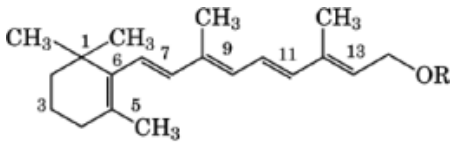


(6)

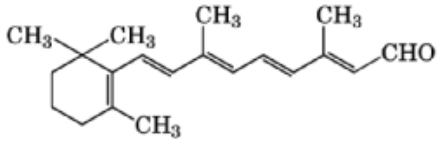
Vitamin A constitutes the most significant sector of the commercial retinoid market and is used primarily in the feed area. In the pharmaceutical area, there are several important therapeutic dermatologic agents which structurally resemble vitamin A and they are depicted in Figure 2 (see Pharmaceuticals). The carotenoids as provitamin A compounds also represent an important commercial class of compounds with β-carotene [7235-40-7] 3 occupying the central role (Fig. 3) (9).

1. Chemical and Physical Properties

Because of the presence of an extended polyene chain, the chemical and physical properties of the retinoids and carotenoids are dominated by this feature. Vitamin A and related substances are yellow compounds which

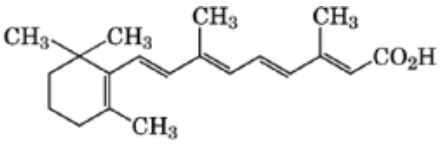


(**1**, R = H)
(**2**, R = CH_3CO)
(**3**, R = $CH_3(CH_2)_{14}CO$)
(**4**, R = CH_3CH_2CO)



(**5**)

Fig. 1. Vitamin A and derivatives: retinol (1), retinyl acetate [127-47-9] (2), retinyl palmitate [79-81-2] (3), and retinyl propionate [7069-42-3] (4).



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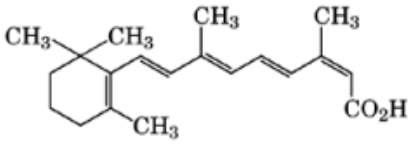
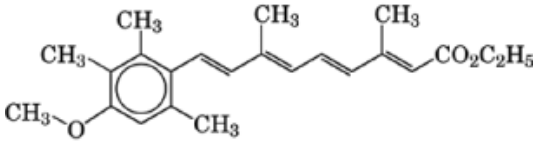


(**8**)



(**9**)

Fig. 2. Commercially important retinoids: retinoic acid [302-79-4] (Tretinoin) (7), 13-*Z*-retinoic acid [4759-48-2] (Isotretinoin) (8), and etretinate [54350-48-0] (9).

are unstable in the presence of oxygen and light. This decay can be accelerated by heat and trace metals. Retinol is stable to base but is subject to acid-catalyzed dehydration in the presence of dilute acids to yield anhydrovitamin A [1224-18-8] **(16)**. Retro-vitamin A [16729-22-9] **(17)** is obtained by treatment of retinol in the presence of concentrated hydrobromic acid. In the case of retinoic acid and retinal, reisomerization is possible

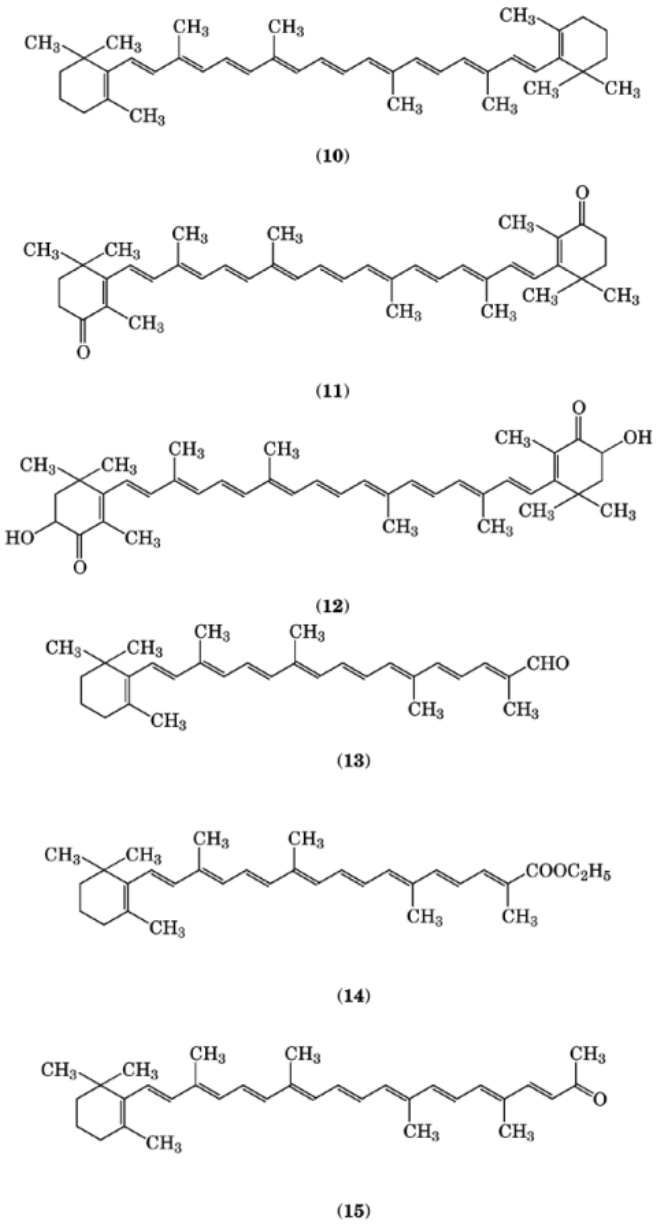


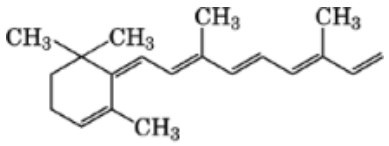
Fig. 3. Commercially important carotenoids: β-carotene (10), canthaxanthin [514-78-3] (11), astaxanthin [472-61-7] (12), β-apo-8′-carotenal [1107-26-2] (13), β-apo-8′-carotenoic acid ethyl ester [1109-11-1] (14), and citranaxanthin [3604-90-8] (15).

after conversion to appropriate derivatives such as the acid chloride or the hydroquinone adduct. Table 1 lists the physical properties of β-carotene [7235-40-7] and vitamin A.

Table 1. Properties of β-Carotene and Vitamin A Derivatives

Property	Retinol[a]	Retinyl acetate[a]	Retinyl palmitate[a]	Retinyl propionate[b]	β-carotene[a]
appearance	crystalline	crystalline	crystalline or amorphous	oil	crystalline
color	yellow	yellow	yellow	light yellow	dark red-dark purple
odor	faint, hay-like	faint, hay-like	faint, hay-like	slight	faint, hay-like
mol wt	286.46	328.50	534.88	342.50	536.85
mol formula	$C_{20}H_{30}O$	$C_{22}H_{32}O_2$	$C_{36}H_{60}O_2$	$C_{23}H_{34}O_2$	$C_{40}H_{56}$
mp, °C	63–64	57–59	28–29		180–182
solubility, g/100 mL					
water	insoluble	insoluble	insoluble	insoluble	insoluble
ethanol	soluble	soluble	soluble	soluble	slightly soluble
isopropanol	soluble	soluble	soluble		slightly soluble
chloroform	soluble	soluble	soluble		soluble
acetone	soluble	soluble	soluble		slightly soluble
fats, oils	750	750	750		0.05–0.08
spectrophotometric properties, nm, max	375[c]	326[c]	325[c]		497,466[d]
fluorescence					
excitation, max, nm	325	325	325		
emission, max, nm	470	470	470		

[a]Ref. 8.
[b]Ref. 10.
[c]Isopropanol.
[d]Chloroform.



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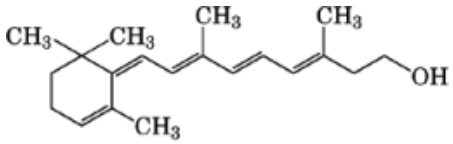

(17)

Of the 16 possible geometric isomers of vitamin A, only the all-trans form has full vitamin A activity and these compounds are commonly named according to the older, nonsystematic nomenclature (Table 2). From a biological standpoint, 11-*cis*-retinal plays a critical role in vision (*vide infra*). As earlier described, 13-*cis*-retinoic acid is important as a dermatological agent. Recently, 9-*cis*-retinoic acid has also been shown to be an important biological isomer and has been identified as a novel endogenous hormone in mammalian tissues (11). The other 13 isomers have no biological or commercial significance. Isolation, characterization, and synthesis of these isomers have been reported (12).

The most conspicuous physical feature of the retinoids and of the carotenoids is the uv spectrum. In the case of the carotenoids, this coloration property is one reason for their commercial significance. In general, there are several factors which influence the position of λ_{max}, the intensity of the absorbance, and the degree of

Table 2. Physical Properties of Stereoisomers of Vitamin A

Isomer	Alcohol mp, °C	λ_{max}, nm	E_{max}	Vitamin A potency, %	Aldehyde mp, °C	λ_{max}, nm	E_{max}	Vitamin A potency, %
all-*trans*-vitamin A	62–64	325	1832	100	57/65	381	1530	91
13-*cis*-vitamin A	58–60	328	1686	75	77	375	1250	93
11-*cis*-vitamin A	oil	319	1220	23	63.5–64.7	376.5	878	48
11,13-di-*cis*-vitamin A	86–88	311	1024	15	oil	373	700	31
9-*cis*-vitamin A	81.5–82.5	323	1477	22	64	373	1270	19
9,13-di-*cis*-vitamin A	58–59	324	1379	24	49/85	368	1140	17

fine structure (13). These include the length of the polyene chain, the number of cis double bonds, and end group functionality. For example, all-*trans*-retinal 1 has an absorption maximum at 368 nm and a molecular extinction coefficient at 48,000, whereas the 7,9,11,13-cis isomer has values of 308 nm and 15,500. Both hypsochromic shifts and hypochromic effects are observed when the stereochemistry of the double bond is changed from trans to cis. External factors such as solvent, temperature, and molecular environments also influence the uv spectra. A striking example of the latter phenomenon is the observed significant bathochromic shift (ca 150 nm) during the association of a carotenoid with a lipoprotein. From a molecular standpoint, the origins of this effect are not completely understood and this remains an area of active research (14, 15).

Other spectroscopic methods such as infrared (ir), ^{1}H and ^{13}C nuclear magnetic resonance (nmr), circular dichroism (cd), and mass spectrometry (ms) are invaluable tools for identification and structure elucidation. Nmr spectroscopy allows for geometric assignment of the carbon–carbon double bonds, as well as relative stereochemistry of ring substituents. These spectroscopic methods coupled with traditional chemical derivatization techniques provide the framework by which new carotenoids are identified and characterized (16, 17).

2. Synthesis

Vitamin A acetate [11098-51-4] 1 is the commercially significant form of the vitamin and is mainly produced by Hoffmann-La Roche, BASF, and Rhône-Poulenc (Fig. 4). All of these processes have β-ionone 4 as their key intermediate and in this regard are based on work performed in the 1940s (18, 19). Their differences lie in methodology to this key intermediate as well as in the methodology to elaborate the side chain. A review of the early work is available (20).

In the process practiced by Hoffmann-La Roche, a $C_{13} + C_1 + C_6$ strategy is employed. In this approach, β-ionone 4 is subjected to a Darzen's condensation to yield the C_{14} aldehyde [116-31-4] 4 (see Fig. 4). Construction of the side chain is completed by a metal acetylide coupling reaction with compound 4. Acetylation, partial reduction of the triple bond, and acid-catalyzed elimination of water completes the synthesis. BASF and Rhône-Poulenc use a different scheme and extend the side chain of β-ionone in an initial step via a Grignard reaction with a metal acetylide. Semihydrogenation yields vinyl β-ionol 4 and it is at this point that the approaches diverge. In the Rhône-Poulenc $C_{15} + C_5$ synthesis, the carbon terminus of vinyl β-ionol is activated by conversion to the sulfone 4. In a second step, the anion of the sulfone is reacted with C_5-chloroacetate 4 to yield vitamin A acetate. BASF utilizes a Wittig olefination and first prepares the phosphonium salt of the C_{15} unit. Reaction of the salt 4 with the C_5 aldehyde 4 leads to vitamin A acetate (21).

Vitamin A palmitate [79-81-2] 1, a commercially important form of the vitamin, is produced from vitamin A acetate 1 via a transesterification reaction with methyl palmitate. Enzymatic preparation of the palmitate from the acetate has also been described (22).

In addition to differences in their methodology to extend the carbon chain, these manufacturers differ in their syntheses of β-ionone. β-Ionone is commercially prepared via an acid-catalyzed rearrangement of

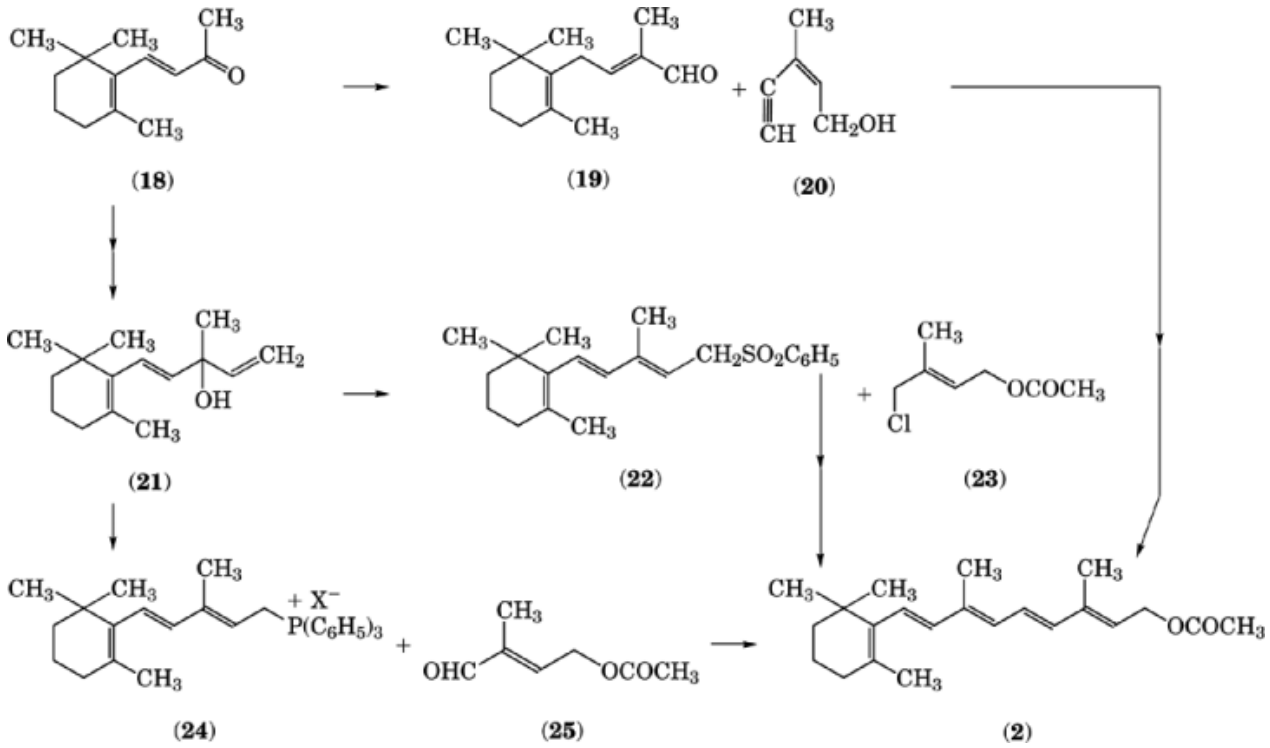

Fig. 4. Commercial synthesis of vitamin A acetate (2).

pseudoionone 5. This intermediate is manufactured on an industrial scale from either citral 5 or dehydro-linalool 5 (21) (Fig. 5).

Citral is prepared starting from isobutene and formaldehyde to yield the important C_5 intermediate 3-methylbut-3-enol 6. Pd-catalyzed isomerization affords 3-methylbut-2-enol 6. The second C_5 unit of citral is derived from oxidation of 6 to yield 3-methylbut-2-enal 6. Coupling of these two fragments produces the dienol ether 6 and this is followed by an elegant double Cope rearrangement (21) (Fig. 6).

The synthesis of dehydro-linalool 5 relies on the basic chemicals acetone and acetylene. Addition of a metal acetylide to acetone yields methylbutynol 7. Semihydrogenation affords the alkene 7 which is reacted with *i*-propenylmethyl ether. A Cope rearrangement of the adduct yields methylheptenone 7. Addition of a second mole of metal acetylide to dehydro-linalool 5 is followed by a second Cope rearrangement to yield pseudoionone 5 (9, 21) (Fig. 7).

In other work, sulfone chemistry plays an integral part of the syntheses of both β-carotene and vitamin A by workers at Kuraray. In this approach, the anion of C_{10} β-cyclogeranyl sulfone 8 is condensed with the C_{10} aldehyde 8. The resulting β-hydroxy sulfone 8 is treated with dihydropyran followed by a double elimination to yield vitamin A acetate. Alternatively, the β-hydroxy sulfone 8 can be converted to the δ-halo sulfone 8 and a similar double elimination scheme is employed (23, 24) (Fig. 8).

Work at Rhône-Poulenc has involved a different approach to retinal and is based on the palladium-catalyzed rearrangement of the mixed carbonate 9 to the allenyl enal 9. Isomerization of the allene 9 to the polyene 9 completes the construction of the carbon framework. Acid-catalyzed isomerization yields retinal 1. A decided advantage of this route is that no by-products such as triphenylphosphine oxide or sodium

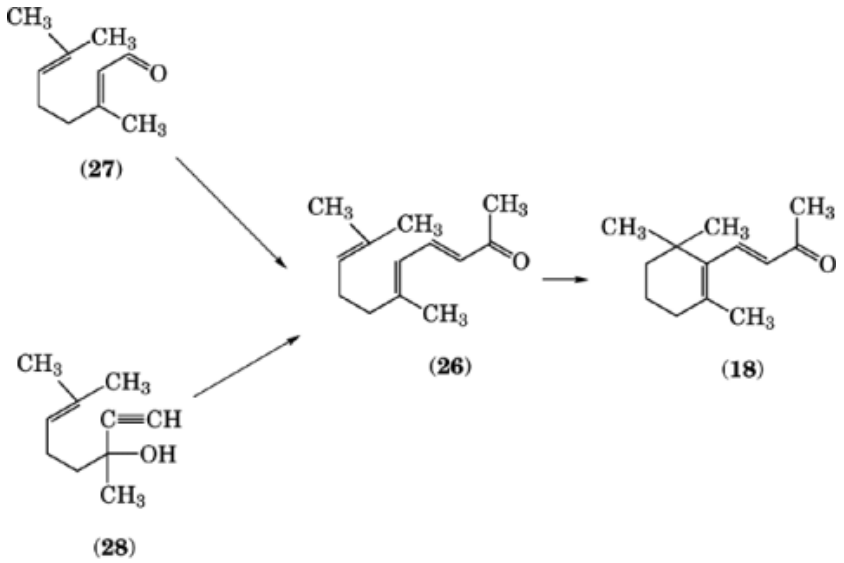

Fig. 5. Industrial approaches to β-ionone (18).

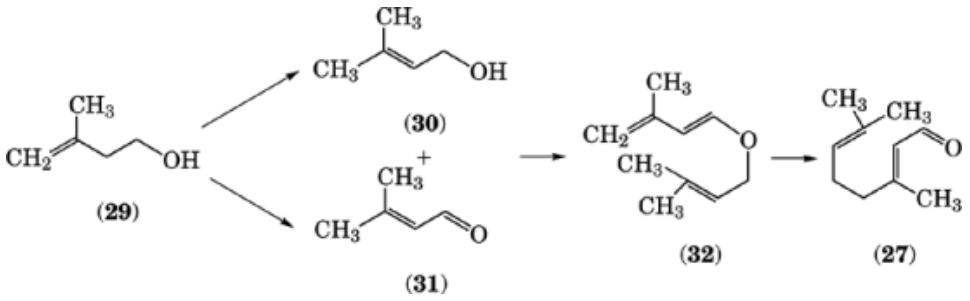

Fig. 6. Synthesis of citral (27).

phenylsulfinate are formed. However, significant yield improvements would be necessary for this process to compete with the current commercial syntheses (25–27) (Fig. 9).

In contrast to the similarities seen in the majority of the industrial syntheses of vitamin A, substantial diversity is observed in the preparations of the carotenoids. Owing to the fact that all-trans stereochemistry is required in the final product and that many olefination reactions yield the cis product, the ease of isomerization at a given locus on the polyene chain has influenced the choice of building blocks. In addition, technological strengths in the construction of these building blocks as well as synergies with a core olefination strength have played an important role in the choice of synthesis.

Hoffmann-La Roche has produced β-carotene since the 1950s and has relied on core knowledge of vitamin A chemistry for the synthesis of this target. In this approach, a five-carbon homologation of C_{14} vitamin A aldehyde 9 is accomplished by successive acetalizations and enol ether condensations to prepare the C_{19} aldehyde 10. Metal acetylide coupling with two molecules of aldehyde 10 completes construction of the C_{40} carbon framework. Selective reduction of the internal triple bond of 10 is followed by dehydration and thermal isomerization to yield β-carotene (21) (Fig. 10).

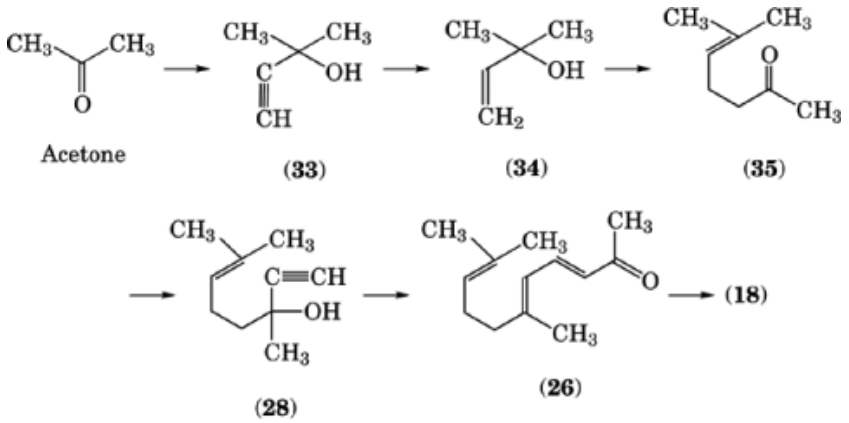

Fig. 7. Acetone-based synthesis of β-ionone.

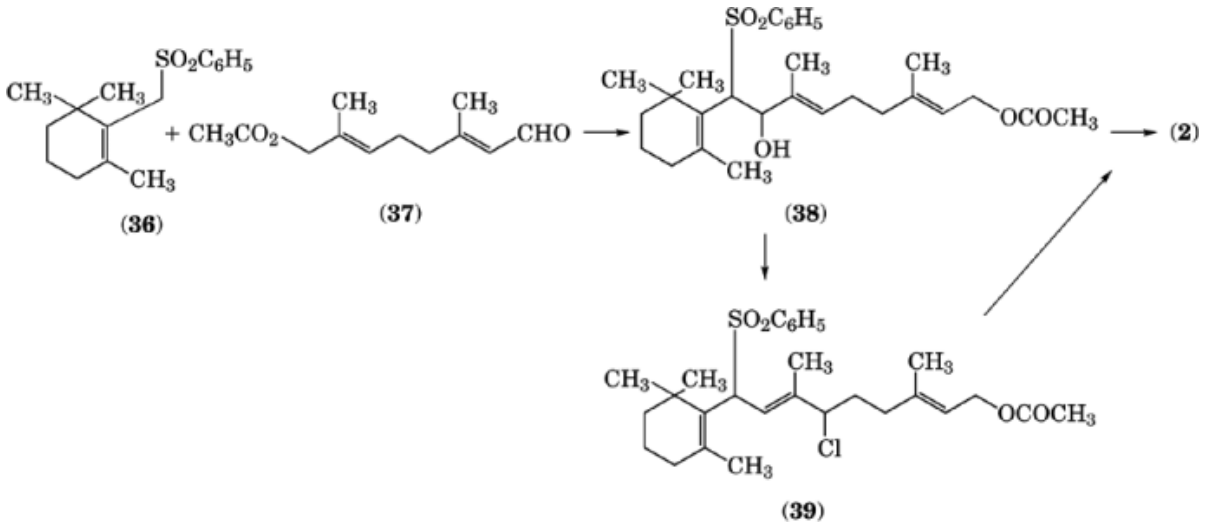

Fig. 8. Kuraray synthesis.

In the BASF synthesis, a Wittig reaction between two moles of C_{15} phosphonium salt (vitamin A intermediate 4) and C_{10} dialdehyde 11 is the important synthetic step (9, 28, 29). Thermal isomerization affords all *trans*-β-carotene (Fig. 11). In an alternative preparation by Roche, vitamin A process streams can be used and in this scheme, retinol is carefully oxidized to retinal, and a second portion is converted to the C_{20} phosphonium salt 12. These two halves are united using standard Wittig chemistry (8) (Fig. 12).

Other approaches to direct C_{20} couplings have been reported (9, 30–35). Based on their knowledge of sulfone chemistry, Rhône-Poulenc has patented many syntheses of β-carotene which use this olefination chemistry (36–41). Horner-Emmons chemistry has also been employed for this purpose (42). The synthetic approaches to the carotenoids have been reviewed (43).

Compounds labeled ^{14}C, ^{13}C, ^{3}H, or ^{2}H are extremely important in understanding the absorption, distribution, metabolism, and excretion of these materials in biological systems. The preparation of these materials has been reviewed (44, 45) and has been the subject of recent investigations (46).

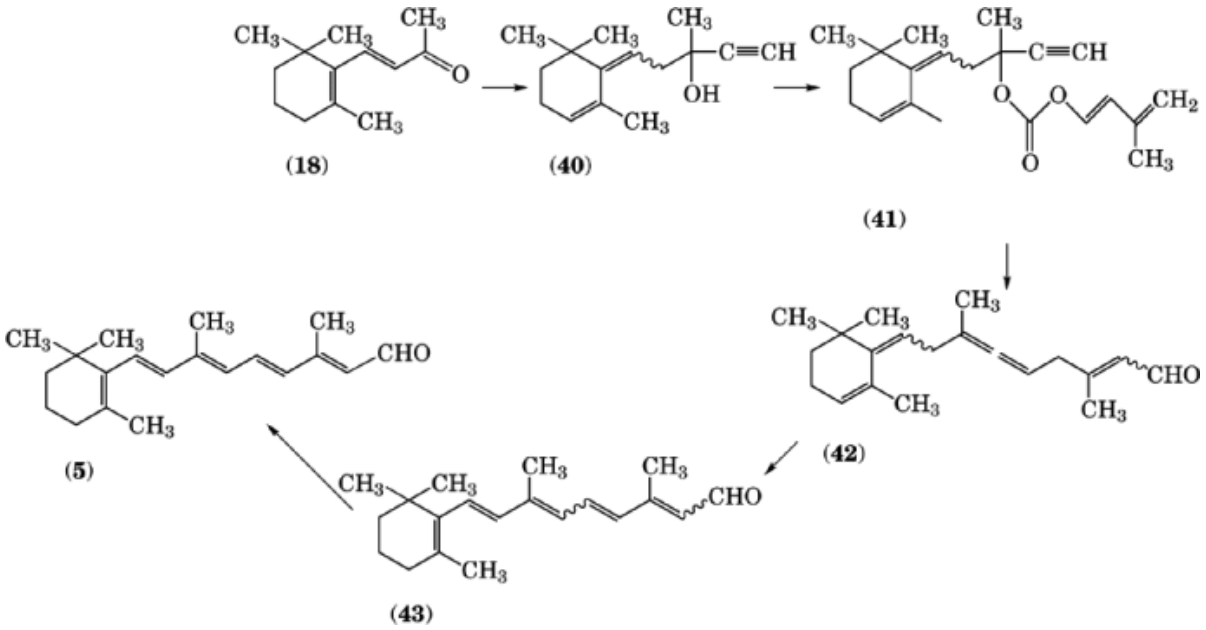

Fig. 9. Allene synthesis of vitamin A aldehyde.

3. Biosynthesis

In nature, vitamin A aldehyde is produced by the oxidative cleavage of β-carotene by 15,15′- β-carotene dioxygenase. Alternatively, retinal is produced by oxidative cleavage of β-carotene to β-apo-8′-carotenal followed by cleavage at the 15,15′-double bond to vitamin A aldehyde (47). Carotenoid biosynthesis and fermentation have been extensively studied both in academic as well as in industrial laboratories. On the commercial side, the focus of these investigations has been to increase fermentation titers by both classical and recombinant means.

The carotenoid skeleton is assembled in a primary step by the coupling of two moles of geranylgeranyl pyrophosphate 13 by an enzyme that is encoded by the *crt B* (carotenogenic) gene. The resulting prephytoene pyrophosphate 13 is further transformed to phytoene 13 possibly by products also derived from the *crt B* gene. Phytoene is a common intermediate in carotenoid biosynthesis. For example, in *E. uredovora* phytoene is converted to lycopene 13 in sequential dehydration steps. These reactions are catalyzed by an enzyme called phytoene desaturase, which is encoded on the gene cluster *crt I*. Interestingly, only *cis*-phytoene and *trans*-lycopene are detected, and it is hypothesized that *trans*-phytoene is formed in a nonenzymatic step. By further biosynthetic transformations, β-carotene 3 is produced from lycopene and zeaxanthin 13 from β-carotene (Fig. 13) (48).

The majority of industrial research describes classical approaches to yield improvement (49). However, there has been some work using genetically modified organisms. In the case of these recombinant organisms, the carotenoid biosynthetic gene cluster has been expressed in noncarotegenic species such as *E. coli* (50) and *S. cerevisiae* (51).

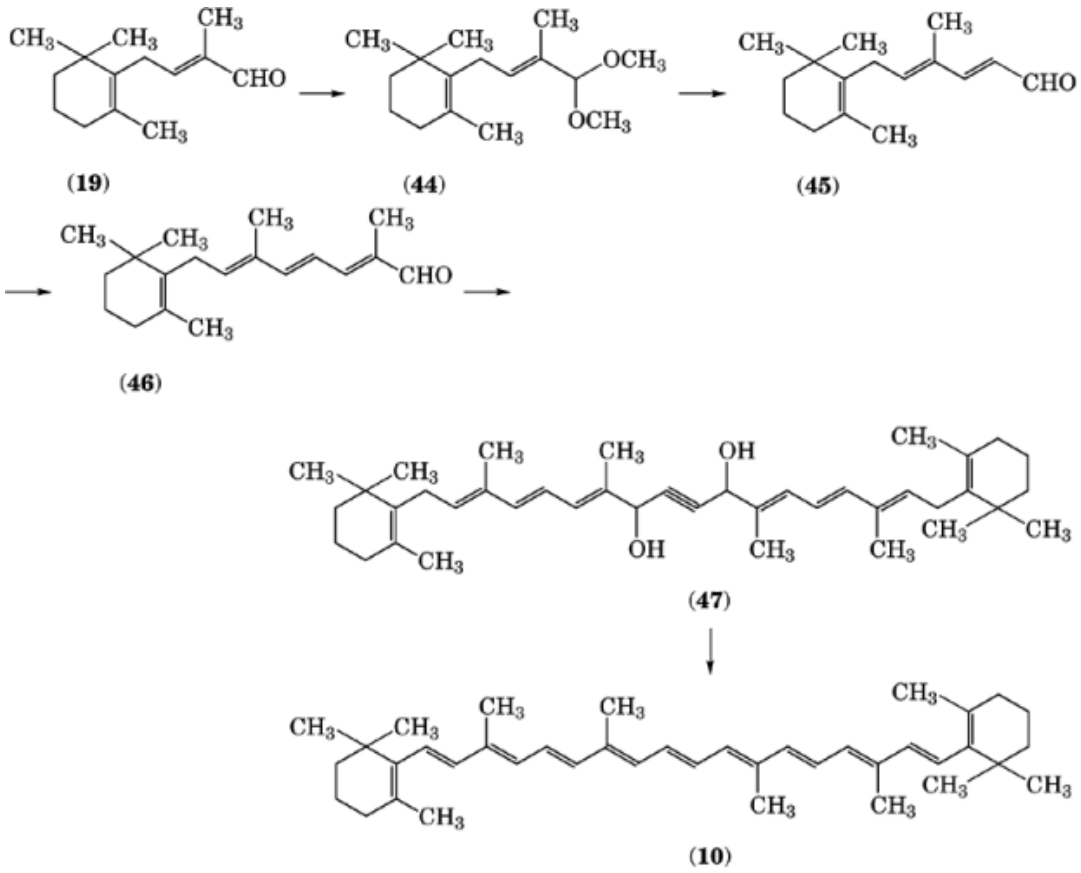

Fig. 10. Hoffmann-La Roche synthesis of β-carotene.

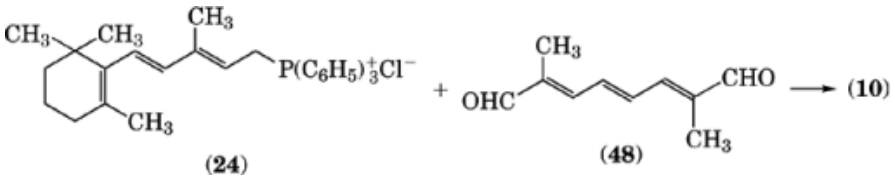

Fig. 11. BASF synthesis of β-carotene.

4. Analytical Methods

Biological, spectroscopic, and chromatographic methods have been used to assay vitamin A and the carotenoids. Biological methods have traditionally been based on the growth response of vitamin A–deficient rats. The utility and shortcomings of this test have been reviewed (52, 53). This test has found applicability for analogues of retinol (54, 55). Carotenoids that function as provitamin A precursors can also be assayed by this test (56).

Spectroscopic methods such as uv and fluorescence have relied on the polyene chromophore of vitamin A as a basis for analysis. Indirectly, the classical Carr-Price colorimetric test also exploits this feature and measures the amount of a transient blue complex at 620 nm which is formed when vitamin A is dehydrated in

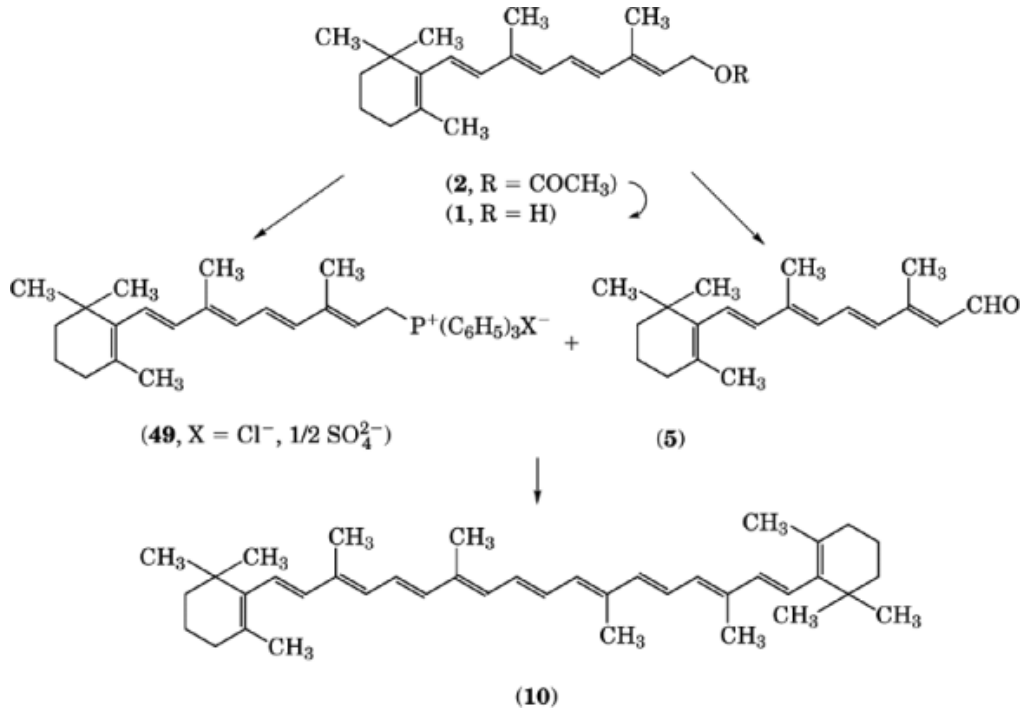

Fig. 12. Alternative Roche synthesis of β-carotene.

the presence of Lewis acids. For uv measurements of retinol, retinyl acetate, and retinyl palmitate, analysis is done at 325 nm. More sensitive measurements can be obtained by fluorescence. Excitation is done at 325 nm and emission at 470 nm. Although useful, all of these methods suffer from the fact that the method is not specific and any compound which has spectral characteristics similar to vitamin A will assay like the vitamin (57).

More specific methods involve chromatographic separation of the retinoids and carotenoids followed by an appropriate detection method. This subject has been reviewed (57). Typically, hplc techniques are used and are coupled with detection by uv. For the retinoids, fluorescent detection is possible and picogram quantities of retinol in plasma have been measured (58–62). These techniques are particularly powerful for the separation of isomers. Owing to the thermal lability of these compounds, gc methods have also been used but to a lesser extent. Recently, the utility of cool-on-column injection methods for these materials has been demonstrated (63).

Owing to the light and air sensitivity of the carotenoids and retinoids, sample handling is a critical issue. It is recommended to conduct extraction of these materials with peroxide-free solvents, to store biological samples at -70°C under argon and in the dark, to perform the analysis under yellow light, and to use reference compounds of high purity (57).

In the *United States Pharmacopeia* (USP), vitamin A content is determined by the ratio of the corrected absorbance to the observed absorbance and is not to be less than 0.85 at 325 nm. Total vitamin A content is to be 95% of label claim. For β-carotene, the assay is performed using uv spectroscopy and is determined by the absorbance at 455 nm. The range of the assay should be from 96.0 to 101.0% (64).

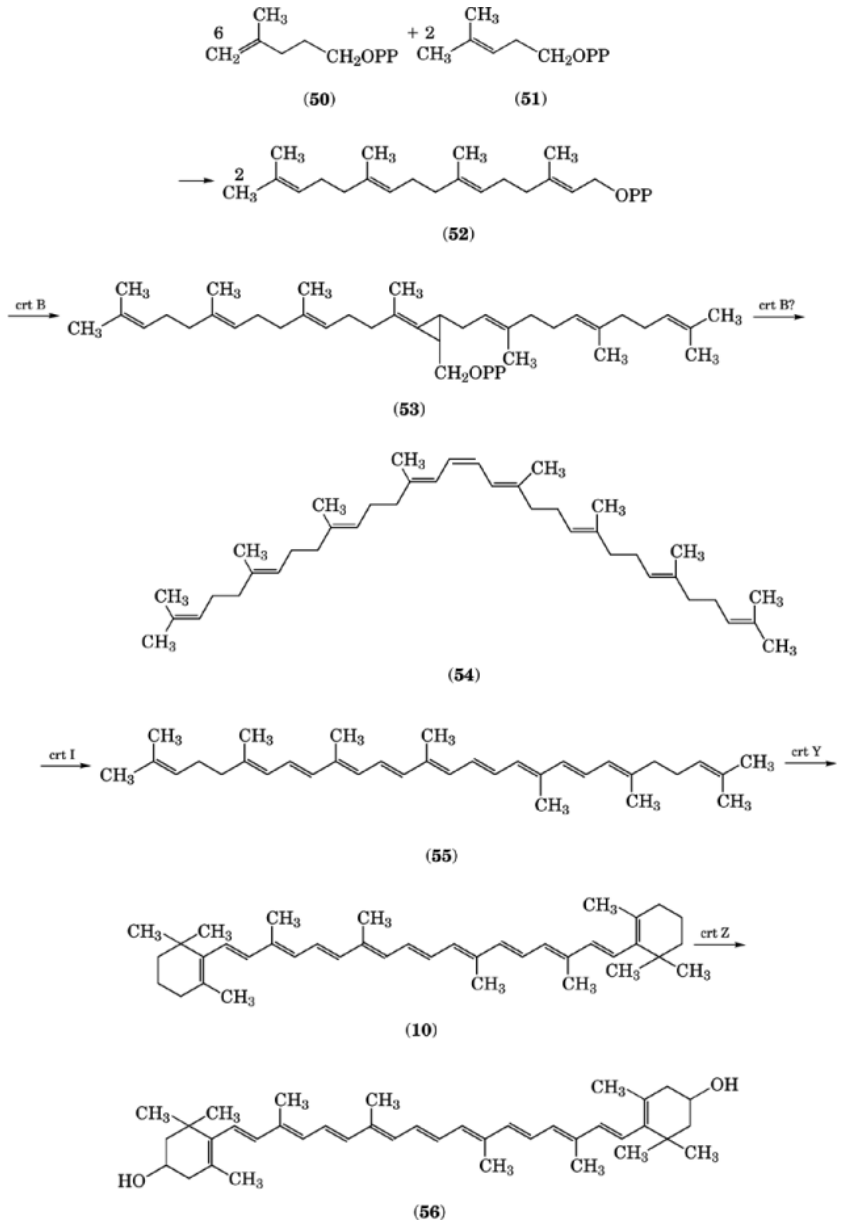

Fig. 13. Biosynthetic transformation of β-carotene.

5. Occurrence

Rich sources of vitamin A include dairy products such as milk, cheese, butter, and ice cream. Eggs as well as internal organs such as the liver, kidney, and heart also represent good sources. In addition, fish such as herring, sardines, and tuna, and in particular the liver oil from certain marine organisms, are excellent sources. Because the vitamin A in these food products is derived from dietary carotenoids, vitamin A content can vary

considerably. Variation of vitamin A content in food can also result from food processing and in particular, oxidation processes (8).

Fertile sources of carotenoids include carrots and leafy green vegetables such as spinach. Tomatoes contain significant amounts of the red carotenoid, lycopene. Although lycopene has no vitamin A activity, it is a particularly efficient antioxidant (see Antioxidants). Oxidation of carotenoids to biologically inactive xanthophylls represents an important degradation pathway for these compounds (56).

6. Biological Functions

In humans, vitamin A has important functions in vision, growth, and tissue differentiation. Its role in vision is fairly well understood and involves initial absorption of all-*trans*-retinol by the pigment epithelium cells of the eye. This event is followed by isomerization to 11-*cis*-retinol by all-*trans*-11-*cis*-retinol isomerase. After conversion of 11-*cis*-retinol to 11-*cis*-retinal, reaction with opsin forms rhodopsin. Absorption of light by this pigment generates the visual signal by cis/trans isomerization. After release of *trans*-retinal from the pigment, *trans*-retinal is rapidly reduced to all-*trans*-retinol and the cycle repeats itself. Consequently, vitamin A is not consumed in the process. One feature of this system is that the basic chemistry is common to many photosensitive systems from such diverse species as halophilic bacteria to higher organisms such as vertebrates (65).

As previously described, the biological assay for vitamin A was based on the growth response of rats fed a vitamin A-deficient diet. Vitamin A is necessary for normal bone growth and remodeling and is required for the activity of epiphyseal cartilage. Retinoic acid is the active form of vitamin A for this function and it has been observed that ingestion of retinoic acid restores growth but cannot maintain vision (8). In animals cycled on retinoic acid, ie, fed a retinoic acid-containing diet then deprived of a retinoic acid-containing diet, these animals become sensitive to the removal of retinoic acid. This condition is characterized by a loss in appetite followed by a depression in growth. As a result, loss of appetite is one of the first symptoms of a vitamin A-deficient animal (8).

The specific role of vitamin A in tissue differentiation has been an active area of research. The current thinking, developed in 1979, involves initial delivery of retinol by *holo*-RBP (retinol-binding protein) to the cell cytosol (66). Retinol is then ultimately oxidized to retinoic acid and binds to a specific cellular retinoid-binding protein and is transported to the nucleus. Retinoic acid is then transferred to a nuclear retinoic acid receptor (RAR), which enhances the expression of a specific region of the genome. Transcription occurs and new proteins appear during the retinoic acid-induced differentiation of cells (56).

In contrast to vitamin A, the carotenoids are important in both plant and animal kingdoms. In plants, carotenoids are associated with photosynthetic structures. The function of these pigments is twofold: (*1*) the pigments serve as acceptors and act as energy-transfer agents and allow for excitation energy to be transferred from the carotenoid to the porphyrin; (*2*) the pigments protect the organism from light-induced photooxidative damage. In this regard, protection is achieved by two mechanisms: quenching of the excited triplet state of chlorophyll (itself a producer of singlet oxygen), and quenching of singlet oxygen. In both cases, a triplet excited state of the carotenoid, which decays back to the ground state by a radiationless conversion, is produced (67).

Many carotenoids function in humans as vitamin A precursors; however, not all carotenoids have provitamin A activity (Table 3). Of the biologically active carotenoids, β-carotene has the greatest activity. Despite the fact that theoretically one molecule of β-carotene is a biological source of two molecules of vitamin A, this relationship is not observed and 6 μg β-carotene is equivalent to 1 μ vitamin A. Although β-carotene and vitamin A have complementary activities, they cannot totally replace each other. Because the conversion of β-carotene to vitamin A is highly regulated, toxic quantities of vitamin A cannot accumulate and β-carotene can be considered as a safe form of vitamin A (8).

Table 3. Provitamin A Activity of Selected Carotenoids[a]

Provitamin A activity	No provitamin A activity
β-carotene	astaxanthin
α-carotene	canthaxanthin
γ-carotene	lutein
β-crypotoxanthin	lycopene
β-zeacarotene	zeaxanthin

[a] Ref. 8.

Table 4. Recommended Daily Allowances of Vitamin A[a]

Sex/age group	1989 RDA (RE)[b]	U.S. RDA (IU)[c]
infants <12 months	375	1500
children		
1–3 yr	400	2500
4–6 yr	500	5000
7–10 yr	700	5000
males ≥ 11 yr	1000	5000
females ≥ 11 yr	800	5000
additional during pregnancy		+3000
additional during lactation		+3000

[a] Ref. 8.
[b] RE = retinol equivalents (1 RE = 1 μg of all-*trans*-retinol).
[c] IU = international units (1 IU = 0.30 μg of all-*trans*-retinol).

Owing to the presence of an extended polyene chain, all carotenoids are effective single-oxygen quenchers and antioxidants. In addition, they can stimulate the immune response and, as a result, may protect against certain forms of cancer. These separate functions, ie, vitamin A equivalents or antioxidants, have allowed for carotenoids to be classified according to whether they are nutritionally or biologically active. For example, β-carotene is both nutritionally and biologically active whereas 14′-β-apocarotenal is nutritionally active but biologically inactive. Lycopene is nutritionally inactive but biologically active, whereas phytoene, the natural precursor to β-carotene, is both nutritionally and biologically inactive (56).

7. Requirements

Animals cannot synthesize vitamin A-active compounds and necessary quantities are obtained by ingestion of vitamin A or by consumption of appropriate provitamin A compounds such as β-carotene. Carotenoids are manufactured exclusively by plants and photosynthetic bacteria. Until the discovery of vitamin A in the purple bacterium *Halobacterium halobium* in the 1970s, vitamin A was thought to be confined to only the animal kingdom (56). Table 4 lists RDA and U.S. RDA for vitamin A (67).

8. Deficiency

In humans, vitamin A deficiency manifests itself in the following ways: night blindness, xerophthalmia, Bitot's spots, and corneal involvement and ulceration. Changes in the skin have also been observed. Although vitamin

A deficiency is seen in adults, the condition is particularly harmful in the very young. Often, this results from malnutrition (56).

On a vitamin A-deficient diet, mucus-secreting tissues become keratinized. This condition tends to occur in the trachea, the skin, the salivary glands, the cornea, and the testes. When this occurs in the cornea, it can be followed by blindness. Vitamin A deficiency is the principal cause of blindness in the very young. This problem is particularly acute in the third world (8).

9. Safety

Vitamin A toxicity can be categorized as either acute or chronic. Acute toxicity results from extremely high doses ($\geq$500,000 IU of vitamin A). In children, approximately half of that amount causes problems. Hypervitaminosis A is characterized by headache, blurred vision, loss of coordination, nausea, and peeling and itchy skin. Chronic vitamin A toxicity occurs in adults with long-term intakes of $\geq$50,000 IU/d. Symptoms include dry hair, hair loss, weakness, headache, bone thickening, enlarged liver and spleen, anemia, abnormal menstrual periods, stiffness, and joint pain. Most of these symptoms are reversible. In animals, extremely high doses of vitamin are teratogenic (56). On the other hand, the carotenoids are generally nontoxic and there have been only a few isolated cases of problems associated with a large daily intake. Tanning pills that contain large doses of canthaxanthin were shown to cause canthaxanthin retinopathy in patients with eryrthropoietic porphyria (68, 70).

10. Uses

Vitamin A is generally used in feeds, foods, and pharmaceutical applications; however, the principal use of carotenoids is as a colorant. β-Carotene, for example, is used to color fat products such as margarine, shortening, butter, cheese, egg nog, and ice cream. It is also used in baked goods, pasta products, juices, and beverages. It imparts a natural yellow to orange shade. Conversely, if an orange to reddish orange color is desired, the carotenoid of choice is β-apo-8′-carotenal [1107-26-2]. This carotenoid is used to color juices, fruit drinks, soups, jams, jellies, and gelatin (qv). Carotenoids are also added to feed to color poultry, fish, and of egg yolks. In order to guard against oxidative damage during feed processing, these compounds are protected in a gelatin matrix as beadlets (see Colorants for food, drugs, cosmetics, and medical devices).

11. Economic Aspects

Vitamin A is manufactured by Hoffmann-La Roche (Switzerland), BASF (Germany), and Rhône-Poulenc (France), as well as by some smaller suppliers in India, China, and Russia. The worldwide production is estimated to be 2500 to 3000 metric tons. About three-quarters of this production is for animal feed; the remainder is for food fortification and pharmaceuticals (qv). The main trade names of feed products are Rovimix, Lutavit, and Microvit. Prices depend on application forms and are approximately \$60–\$70/10^9 IU retinol (1995); ie, \$200–\$233/10^9 RE. One IU is equivalent to 0.300 μg of all-*trans*-retinol and 1 RE is equivalent to 1 μg of all-*trans*-retinol.

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SUSAN D. VAN ARNUM
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