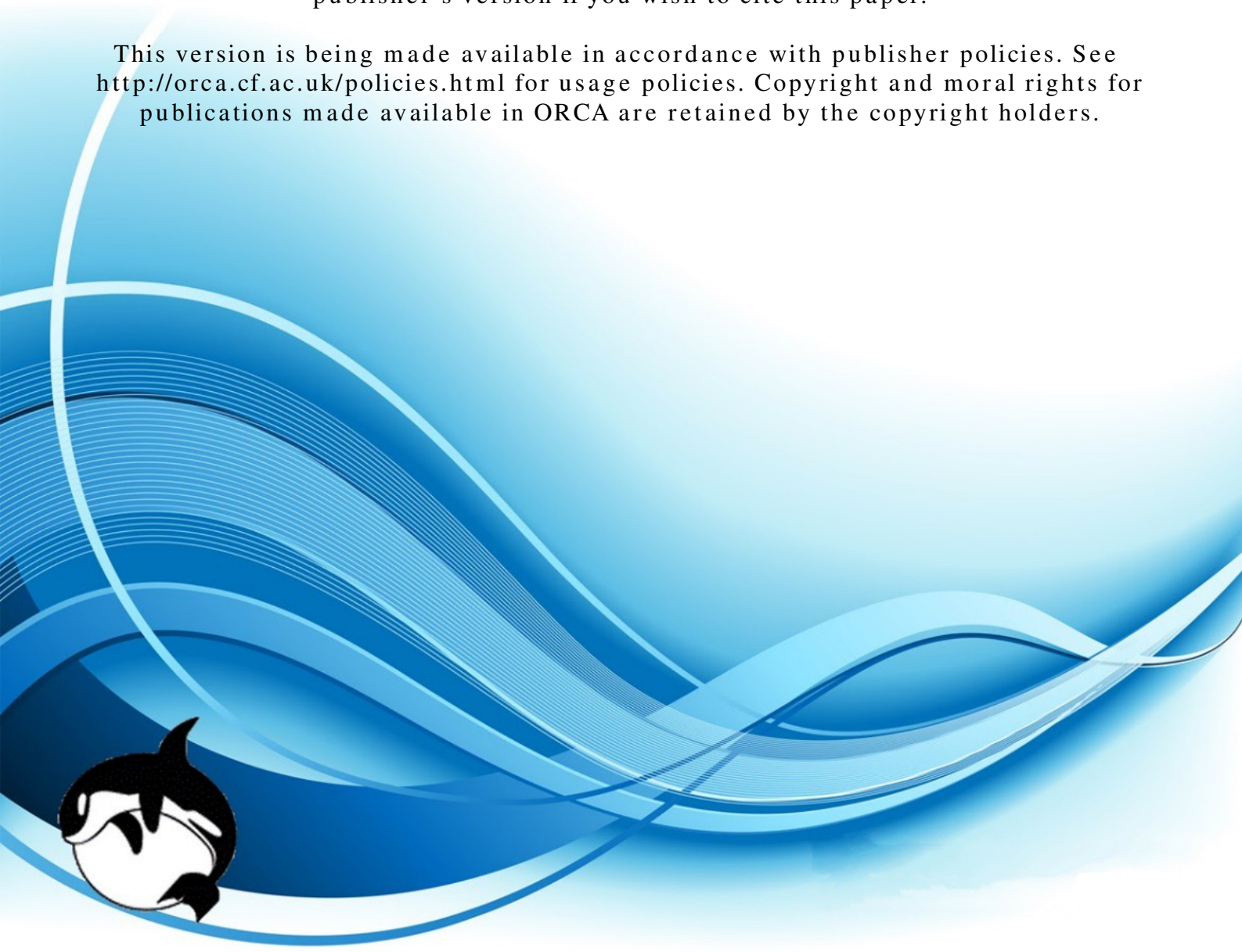

A Review of Stability Issues Associated with Vitamins in Parenteral Nutrition

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Abstract

Background & aims: There has been a move to increased emphasis on delivering parenteral nutrition to patients at home, which may improve patient care and reduce costs. However, safe provision of home, and indeed any, parenteral nutrition necessitates consideration of the physical and chemical stability of the parenteral nutrition and its components.

Methods: Medline and Embase were used to search for all English-language publications on vitamin stability. Identified publications were then analysed and summarised in the following review.

Results: Vitamins are one of the least stable components in PN and there are three main ways in which they have been shown to degrade: photodegradation, oxidation and through storage material interaction. Previous research on vitamins has demonstrated that significant losses can occur in the bag, which could have clinical consequences, particularly for long-term users of parenteral nutrition. These losses are most dramatic for vitamin C, which is rapidly degraded by oxygen, and vitamin A, which is rapidly degraded in the presence of sunlight.

Conclusions: There are a number of stability issues associated with vitamins in parenteral nutrition and further investigation is needed to assure their stability and compatibility with other parenteral nutrition constituents.

Key words

Parenteral Nutrition, Vitamins, Stability, Degradation

Introduction

Historically, Parenteral Nutrition (PN) was prepared at ward level in a multi-bottle dose system[1]. This method was labour intensive and was readily susceptible to contamination. This called for the introduction of an all-in-one (AIO) bag, which would decrease the incidence of infection and be a convenient and cost-effective alternative to the multi-bottle system previously employed[1–3]. The use of an AIO bag meant that all macronutrients, vitamins, trace elements and electrolytes were introduced to the same bag prior to administration, leading to a number of formulation and stability issues.

At present, there is a drive within the NHS to treat patients at home in an attempt to significantly reduce costs and improve clinical outcomes[4,5]. An increased emphasis on delivering treatments at home has stimulated researchers to investigate the sources of instability within PN admixtures, thereby validating shelf lives and allowing more convenient administration at home.

One aspect of PN that has not been fully investigated is the addition of vitamins. Vitamins are highly reactive and their addition to PN admixtures can cause a number of pharmaceutical issues. Reactions involving vitamins are dependent on: relative concentrations of reactants, pH, temperature, time, container material and the presence of any other catalytically active components[6]. The reactive nature of vitamins mean they should be added shortly before administration to ensure that the integrity of the admixture is

maintained[7]. There are three main types of vitamin instability seen in PN: photodegradation, oxidation and interactions with storage material[8]. In every PN admixture administered a patient should receive a days supply of vitamins and trace elements[9]. Ensuring that patients are administered with sufficient amounts of vitamins is essential for normal bodily function and to prevent the manifestation of clinical symptoms of deficiency. Water-soluble vitamins in particular require regular dosing as they are not stored in significant amounts in the body, with the exception of vitamin B_{12}. Ensuring adequate dosing of fat-soluble vitamins is also important especially in patient groups such as infants, who only have small quantities of fat-soluble vitamins stored[10].

Stability problems encountered with PN admixtures can occur in containers or administration sets. This is especially problematic for premature infants who receive their PN at slow infusion rates[10]. These stability issues can prevent patients from getting their intended doses or may harm the patient either through generation of potentially harmful by-products or interfere with the physical stability of the admixture[8]. A better grasp of how vitamins interact with the environment they are stored in and other PN components will ensure the safe use of them in the future.

The following review examines the current information available on the stability issues associated with vitamins.

Fat Soluble Vitamins

Vitamin A

Vitamin A, or retinol, is the most light-sensitive micronutrient found in PN admixtures. When subjected to light in unprotected bags or administration sets, it undergoes extensive photodegradation[11–13]. The mechanism of this reaction is still not fully understood, but it is known that the wavelength and the intensity of the light interacting with the vitamin determines the rate of the photochemical reaction[12]. A study by Allwood and Plane[14] showed that retinol is more susceptible to photodegradation when exposed to wavelengths of less than 400 nm, with maximum degradation occurring between 330-350 nm. Such wavelengths are more commonly found in natural daylight, with artificial light emitting smaller amounts of wavelengths in the UV range[12]. Nevertheless, a recent study by Ferguson et al.[15] has found significant degradation (in excess of 10%) when retinol is exposed to artificial lighting that would be commonly found in hospitals and homes: cool white light and warm white light.

The inclusion of lipid in all-in-one (AIO) admixtures has resulted in the opacity of the admixture being increased significantly. There have been conflicting reports[13,16], but the addition of lipid does not seem to provide sufficient protection for light sensitive vitamins such as retinol[12]. Therefore, to assure retinol photostability in PN light-protective covers should be used.

Since these studies on retinol degradation were performed there has been a change in lighting preference, with a number of aseptic units using energy-saving light bulbs. Similar changes have also occurred in homes in an attempt

to reduce costs. The impact of this change in lighting on retinol degradation has not yet been investigated fully. Until more is known about its influence on the degradation of retinol the use of light protection is essential[17].

Besides photodegradation, sorption of retinol may occur with bags and administration set tubing, further reducing the amount of vitamin being administered to the patient[8]. This problem has been much reduced through the use of the less reactive palmitate ester, rather than the acetate ester[10]. The introduction of tubing containing polyolefine, which is free of PVC, plasticisers, adhesives or latex, has further reduced the absorption of vitamin A[18].

Another source of degradation of vitamins are peroxides generated by lipid emulsions. Lipid emulsions containing polyunsaturated fatty acids (PUFAs) are at an increased risk of peroxidation[19]. Vitamin E acts as a major scavenger for free radicals and prevents lipid peroxyl radicals from reacting with fatty acid side chains[20]. Nevertheless, peroxiodation still occurs to some degree. Guidetti et al.[21] have studied the impact of different lipid emulsion compositions on vitamin degradation via peroxidation. Following 24 hours of light protected storage at room temperature Guidetti et al. found that retinol recovery was significantly increased in soybean-medium chain triacylglycerol oil-based emulsions when compared to soybean oil-based emulsions and olive/soybean oil-based emulsions. Further investigation is required to understand the relationship between the composition of lipid emulsions and the degradation of vitamins.

Vitamin D

As described by Allwood and Kearney[8], there are very limited stability data available for vitamin D in PN. The only study on this vitamin has shown that following a 24-hour infusion period, 68% of the vitamin D concentration was recovered. Comparison of sample concentrations at various sites within the infusion set-up suggested that vitamin D may bind to plastic found in bags and administration sets[22].

There has been a lot of recent interest in vitamin D, especially with the re-emergence of rickets in some urban areas. Consequently, there has been a call to increase its recommended daily allowance in countries such as the United States of America and Canada[23]. This may, in turn, lead to an increase in the recommended amount of vitamin D being given to PN patients.

Vitamin E

Vitamin E is degraded by oxygen in a reaction catalysed by light. The intensity and wavelength of light as well as the amount of oxygen available influences the rate of degradation. Vitamin E is particularly sensitive to wavelengths between 285 nm and 305 nm[24].

Vitamin E seems to be relatively stable in admixtures especially when protected from light[11–13,25]. A study by Allwood and Martin[12] investigated the

effect of light exposure on PN admixtures in multi-layered bags. They found that if oxygen was prevented from permeating into the bag, exposure to sunlight did not significantly reduce the concentration of vitamin E in the admixture. Additionally, in the presence of ascorbic acid, vitamin E oxidization is decreased as these two vitamins compete for oxygen[12].

Guidetti et al.[21] also investigated the impact of lipid emulsion composition on tocopherol degradation. Like retinol, this study found that the recovery of both of the vitamin E isomers examined, α-tocopherol and γ-tocopherol, were significantly increased in AIO bags containing soybean-medium chain triacylglycerol oil-based emulsion when compared to soybean oil-based emulsions and olive/soybean oil-based emulsions.

It is important to note that vitamin E is commonly presented as a mixture of eight tocopherol isomers and the stability profiles have not been determined for each of the isomers. The introduction of increased levels of tocopherol in an attempt to protect fish oils found in some PN from oxidation, necessitates a thorough understanding of tocopherol isomer stability profiles[26].

Vitamin K_1

Phylloquinone (vitamin K_1) is a naturally occurring compound synthesized in plants. As it develops naturally in lipid emulsions some emulsions have higher concentrations than others[27], so patients may receive different amounts. However, reports of the impact of phylloquinone levels on neonates suggest

that symptoms associated with increased levels (e.g. constipation and pain) are non-serious and self limiting[28].

Phylloquinone is sensitive to sunlight but is considered stable in PN mixtures in the presence and absence of lipid emulsions, supporting the theory that lipid emulsions have little, if any, protective influence on light sensitive vitamins. It has been reported that the concentration of phylloquinone can decrease by 50% following 3 hours in strong sunlight[13]. Another study has shown degradation of 5.9-8.5% over 4.5 hours in artificial daylight[29].

Water Soluble Vitamins

Ascorbic acid

Vitamin C is one of the most reactive vitamins added to PN admixtures. In the body it is a strong antioxidant that quenches reactive oxygen and nitrogen species[30]. When stored outside of the body, ascorbic acid acts in a similar way, reacting readily with oxygen. As shown in figure 1., ascorbic acid in the presence of oxygen is initially converted, by way of a reversible reaction, to an equally biologically active compound called dehydroascorbic acid. Hydrolysis of dehydroascorbic acid produces 2,3-diketo-gulonic acid, which is thought to be biologically inactive. Further oxidation of this intermediate produces threonic acid and oxalic acid. The degradation of ascorbic acid is directly linked to the amount of oxygen present in the medium[31]. Exclusion of free oxygen from the PN admixture limits the initial conversion of ascorbic acid to dehydroascorbic acid, thereby minimizing the resultant cascade[32]. Oxygen in

PN bags can originate from permeation of air through the bag wall during storage, residual headspace formed following filling and sealing and from dissolved air in injections of additives and infusions. The use of multilayered AIO bags has significantly reduced the amount of oxygen able to diffuse into the bags, thereby improving ascorbic acid stability[8]. However, this development has not eliminated the problem completely as oxygen transferred into the bag during filling cannot diffuse out of the bag and therefore remains in contact with the vitamin.

Additives to PN not only accommodate the transfer of oxygen to the medium, but also can directly influence ascorbic acid degradation. Copper, and to a lesser extent manganese, zinc and ferric ions, catalyse the oxidation of ascorbic acid to dehydroascorbic acid[32]. This theory has recently been supported by an extensive study conducted by Ferreyra et al.[33] who found significant degradation of ascorbic acid following the addition of nine trace elements to two-in-one (TIO) PN bags when compared to bags with no trace element additions. With copper, vitamin C is oxidized causing the concomitant reduction of copper from the cupric (II) to the cuprous (I) form. As a result of this, the cascade and the eventual production of threonic acid and oxalic acid speeds up. This reaction is enhanced by the introduction of such ions present as trace contaminants in PN components, resulting in higher concentration of copper available to catalyse the degradation of ascorbic acid[34]. Allwood[35] investigated compatibility and stability in 3 Litre bags and found that the amino acid cysteine inhibits the catalytic effect of copper. Therefore, inclusion of

cysteine in amino acid solutions may be beneficial in slowing the degradation of ascorbic acid.

Physical conditions such as temperature and pH can also influence degradation of ascorbic acid in PN: at higher temperatures ascorbic acid degradation is increased[36,37] and pH values above 4.0 make ascorbic acid more susceptible to oxidation[30].

The products of ascorbic acid degradation, oxalic acid and threonic acid, may compromise the stability of the emulsion by increasing the acidity. pHs below 5 can destabilize the PN emulsions[38]. In addition, oxalic acid interacts with free calcium to produce calcium oxalate precipitate[6]. The impact of calcium oxalate formation in adults is unresolved but it is known to be hazardous to neonates[31]. Further investigation into the additional risks posed by oxalic acid and its precipitate is required.

Thiamine

In the past, thiamine in PN was degraded mainly by means of a reduction reaction. Sodium metabisulphite, a common antioxidant used in older generations of amino acid infusions, readily reacts with thiamine in solution[8]. This reaction involves the cleavage of thiamine molecules by sulphite into pyrimidine and thiazole. The stability of thiamine was directly linked to the concentration of sodium metabisulphite. Sodium metabisulphite is no longer

routinely used, with no amino acid solutions available in the UK containing it. Removal of this antioxidant has increased the stability of thiamine[39].

Riboflavin

Riboflavin has long been thought to degrade when it is exposed to daylight. In the presence of light and oxygen, riboflavin is irreversibly converted to luminoflavin and luminochromo, amongst other compounds[6]. A recent study by Ferguson et al.[15] found significant degradation (in excess of 10%) of riboflavin when exposed to cool and warm white artificial light over a period of 24 hours. Significant degradation was also observed in a study by Mirkovic et al.[40] following 12 hours of exposure of riboflavin to daylight. In contrast, studies by Dahl et al.[11] and much more recently by Ribeiro et al.[6] have shown no significant losses when stored at 25°C for 3 days and very little riboflavin loss when stored over a period of up to four days with and without light protection. However, the nature of the room illumination is not stated in any of these studies, so its influence is not quantifiable.

One of riboflavin's more undesirable properties is that it can act as a photochemical sensitizer[41]. As shown in figure 2., when riboflavin is in an excited state it can react directly with substrates or aid in the production of reactive oxygen species. Production of such reactive species may in turn, cause the oxidation of other PN constituents. Investigations into the effects of this process on various components of PN are ongoing[42–44].

Pyridoxine

Pyridoxine is known to be light sensitive, although, there is limited information available on its stability in admixtures. It has been reported to be stable in PN admixtures for up to 96 hours at 2-8°C in darkness[11]. Chen et al.[45] reported an 86% loss of pyridoxine occurring in 8 hours of direct sunlight. A more recent study by Ribeiro et al.[6], found that pyridoxine was stable for 3 days when stored between 4°C and 25°C with and without photo-protection. Again, the illumination of the room in which the samples were stored is not stated therefore it is difficult to ascertain the extent of its influence on degradation.

Juhasz et al.[46] examined the thermal decomposition of pyridoxine. In this experiment, they calculated the amount of time it takes to reach 90% pyridoxine recovery at 25°C to be $1.7x10^{-2}$ years (approximately 6.2 days). This experiment was conducted using a pure sample of pyridoxine and may not correspond to pyridoxine degradation in parenteral nutrition.

Folic acid

There are very few studies investigating the degradation of folic acid. The main source of instability arises from changes in pH. Folic acid injections are usually formulated at a pH in excess of 8.0 because the vitamin is prone to precipitation at lower pHs[47]. One investigation examined the effect of pH on folic acid precipitation and found that if the pH remains above 5.0, folic acid

remains in solution[48]. As PN usually has a pH of between 5.0-6.0, folic acid should not precipitate.

There has been a suggestion by Lee et al.[49] that adsorption of folic acid onto polyvinylchloride (PVC) infusion bags may occur and was responsible for a 33% loss seen after 42 days of storage. However, later studies have found the vitamin to be compatible with PN bags[11,48].

Nicotinamide, Pantothenic acid, Biotin and Cyanocobalamin

There is very limited information available on the stability of cyanocobalamin, pantothenic acid, biotin and nicotinamide in PN. Dahl et al.[11] report that all four are stable in PN admixtures when stored for 96 hours. However, as no further studies have been reported, the stability of these water-soluble vitamins requires further investigation.

Conclusion

The inclusion of vitamins in PN provides a number of formulation issues. Ascorbic acid is the most unstable vitamin added to PN and is degraded by oxygen into a number of different products including oxalic acid. There is some concern over the formation of oxalic acid, which may form a calcium oxalate precipitate. Further investigation into its impact is required.

Photodegradation is a problem encountered with vitamins such as retinol and can cause significant losses. In addition, the impact of light on degradation in giving sets is an important consideration as the surface area of PN in contact with light is vastly increased.

The role of riboflavin as a photochemical sensitizer is being explored.

Its ability to form reactive oxygen species may have a significant impact on the stability of PN as a whole.

Little is known about the stability of vitamins such as nicotinamide, cyanocoabalamin, biotin and pantothenic acid in PN. Clearly this needs some further investigation.

Trace elements can also cause a number of problems during compounding and administration. A recent paper by Hardy et al.[34], is an excellent review of the current literature available on trace elements.

Many of the degradation processes of vitamins in PN admixtures can be reduced or prevented by controlling physical conditions. Light exposure can cause degradation of a number of water and fat-soluble vitamins, most notably riboflavin and retinol. Use of light protection on bags and

administration sets can reduce vitamin loss significantly. Degradation can be further reduced in administration sets through shortening the lines to the patient. This would decrease degradation caused by light sources and also help to decrease vitamin sorption onto the tubing[10]. The light protective effects of lipids on vitamins is a contentious issue that needs further investigation, nevertheless, the use of lipid may provide added protection for light sensitive vitamins. Oxygen is another problematic physical condition that is the cause of substantial vitamin degradation, with ascorbic acid being the worst affected. Use of multi-layered bags and removal of excess air after filling reduces degradation rates even in the presence of trace elements. The use of cysteine may also help inactivate copper catalysis of ascorbic acid oxidation to its degradation product dehydroascorbic acid.

This review illustrates the importance of vitamin stability in parenteral nutrition. Maintaining vitamin stability will ensure that patients receive the correct doses and prevent the production of potentially harmful degradation products. Furthermore, it shows that there is still plenty of research to be done on vitamin stability in parenteral nutrition admixtures.

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Statement of authorship

TF prepared the first draft of the review. TF, SE, RPD and AGC contributed to the final version of the review. All authors have made substantial contributions to and approved the final version of the review.

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Figure 1. The ascorbic acid degradation cascade adapted from Allwood and Kearney[4].

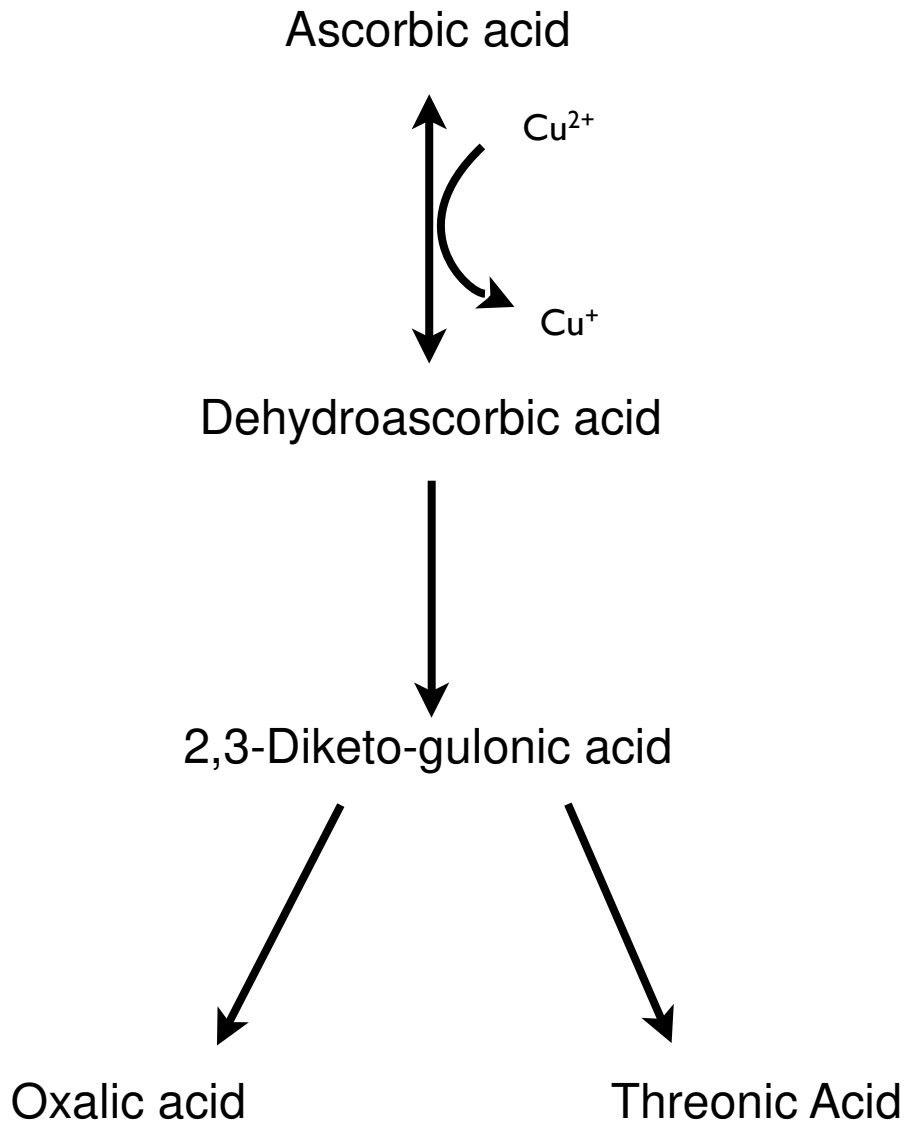

Figure 2. A flow diagram illustrating riboflavin as a photosensitizer.

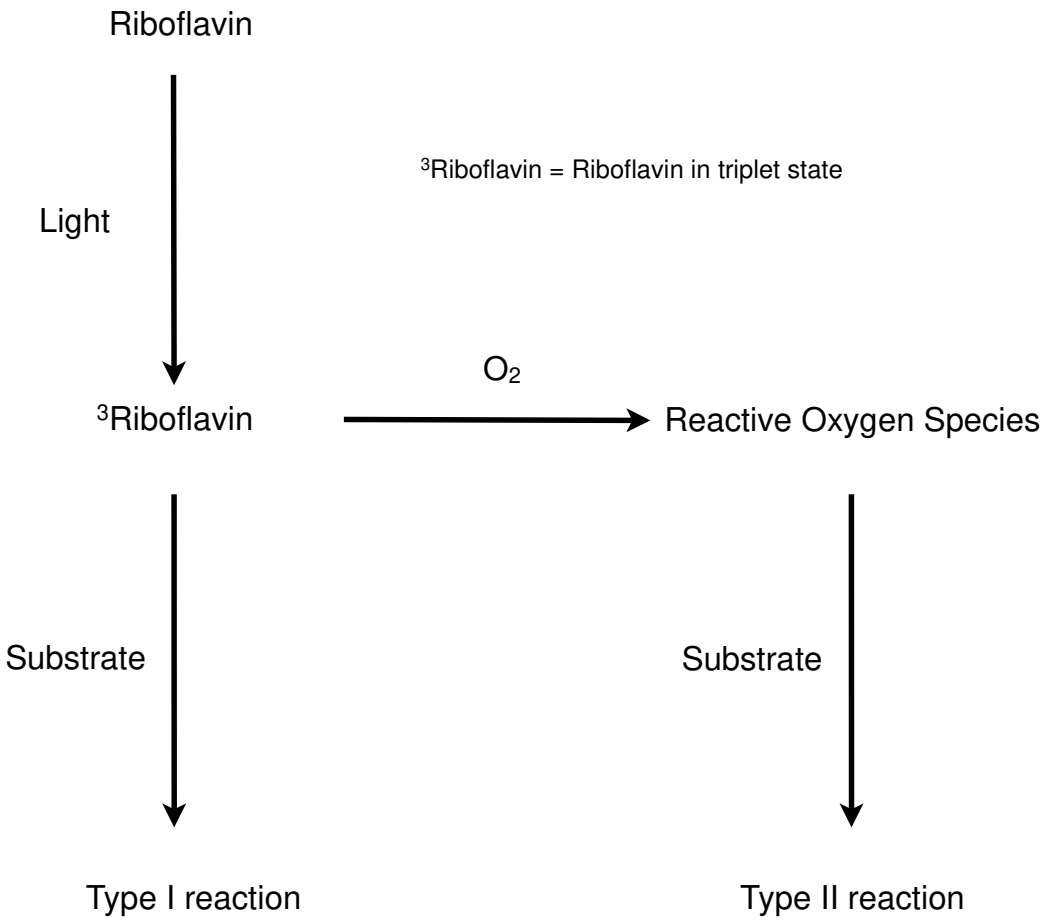

Table 1. Vitamin Reference Nutrient Intake (RNI) values for healthy males and females aged between 19-50 years adapted from Department of Health reference values for Food Energy and Nutrients for the United Kingdom (41):

Vitamin	Males 19-50 years	Females 19-50 years
Vitamin A	700 μg/day	600 μg/day
Vitamin D	-	-
Vitamin E	Above 4 mg/day	Above 3 mg/day
Vitamin K	1 μg/kg/day	1 μg/kg/day
Ascorbic Acid	40 mg/day	40 mg/day
Thiamine	1 mg/day	0.8 mg/day
Riboflavin	1.3 mg/day	1.1 mg/day
Niacin	17 mg/day	13 mg/day
Pantothenic acid	3-7 mg/day	3-7 mg/day
Pyridoxine	1.4 mg/day	1.2 mg/day
Biotin	10-200 μg/day	10-200 μg/day
Folate	200 μg/day	200 μg/day
Cyanocobalamin	1.5 μg/day	1.5 μg/day

N.B. Niacin describes the total amount of nicotinic acid and nicotinamide in the diet.

Table 2. Quick reference of known physical vitamin sensitivities:

Vitamin	Light	Oxygen	pH	Temperature
Vitamin A	✓			
Vitamin D				
Vitamin E	✓	✓		
Vitamin K	✓			
Ascorbic acid		✓	✓	✓
Thiamine				
Riboflavin	✓			
Nicotinamide				
Pantothenic Acid				
Pyridoxine	✓			
Biotin				
Folic Acid			✓	
Cyanocobalamin				