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Food Preservation with EDTA
Particularly of interest for omega-3 enriched products?

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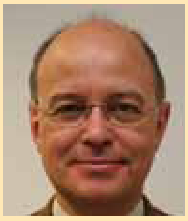


Carel T. J. Wreesmann

ABSTRACT: The synthetic food additive EDTA (ethylenediaminetetraacetic acid) has been allowed in the USA since 1964 and throughout the entire EU since 1995. With the current rising interest in omega-3 fatty acids and their benefits to health, the need for an effective shelf-life enhancing agent is becoming increasingly more urgent. Of all fatty acids the omega-3's are most sensitive to deterioration during storage. Of all shelf-life enhancing agents EDTA has been observed to be among both the most effective and safest food additives that have ever been introduced. Particularly with respect to prevention of rancidity of food products enriched with omega-3's, the use of EDTA has been found to be highly advantageous. Regulatory adaptations are discussed that could allow a broader use. In this way we may enjoy an even healthier diet in the near future through a more appropriate intake of omega-3 fatty acids.

EDTA IN FOODS

"No longer a chemical curiosity, EDTA has taken its place among other stabilizers as a full-fledged tool of the food industry. Colourless, odourless and tasteless, strikingly effective as a metal sequestrant in many applications, EDTA can be expected to receive more attention from food scientists in the future". This is what Thomas E. Furia wrote down in a still highly worthwhile review on "EDTA in Foods" back in 1964 (1). He wrote this article to accompany the US FDA approval in that very same year of both disodium and calcium disodium EDTA in food. By no means could Dr. Furia foresee, as outlined further down, what this "more attention" would all entail in the decades to come.
However, with the currently increasing interest in omega-3 fatty acids EDTA can be expected indeed to receive more attention from food scientists again.

Early History of EDTA

EDTA was invented at the end of the 1930's in Germany by IG Farbenindustrie. Its first use was to improve the process of textile dyeing thanks to its water softening properties (2).
In the 1940's Prof. Gerold Schwarzenbach and his team in Zurich, Switzerland contributed largely to a better understanding of the strikingly strong metal-binding characteristics of EDTA (3).
Directly after World War II, the major developments around EDTA were in the USA. The pioneering chemist Frederick C. Bersworth came up with a superior manufacturing route for EDTA, which is still widely used to-date and unveiled a large number of new applications (2). And last but not least, the use of metal-EDTA's and related metal complexes as trace mineral fertilizers in agriculture originates from those days in the USA as well (4).
As a heritage from World War II, a lot of people in the USA suffered from health problems caused by to contamination with lead and radioactive metals. Soon it was discovered that intravenous administration of EDTA provided an effective and safe remedy against these life-threatening conditions. It was in the US Los Alamos Research Centre where some major investigations were preformed that clearly underlined the amazingly high level of "human-friendliness" of EDTA (5).

Recent history of EDTA

What Thomas Furia could not foresee in his review in 1964 (see above) was, apart from the use of EDTA in omega-3 enriched food products, the issue of biodegradability and the promise of EDTA in the form of ferric sodium EDTA (FeNa-EDTA) as an opportunity to cure anaemia.

EDTA in drinking water

As outlined below EDTA disappears only slowly from surface waters into which treated sewerage water has been drained. As a consequence, minute traces of EDTA may end up in our drinking water. And this was observed to happen in the 1970's. EDTA was the first man-made compound ever to be hit by this fate, causing quite a shock amongst decision makers and opinion leaders in those days. Many more compounds of man-made origin, many of them being break-down products of medicines and pesticides, have been detected since in our drinking water.
Although this concern about drinking water contamination is fully justified, the presence of ppb levels of EDTA in drinking water can be considered as harmless (6).

EDTA to cure anaemia

In the 1970's it also became clear that EDTA in the form of FeNa-EDTA could play a role in fighting anaemia in this world through food fortification. FeNa-EDTA can be added to many food products without inducing undesired taste effects, but nevertheless giving rise to a desirably high level of iron absorption comparable to that of red meat. Fortification of staple foods with FeNa-EDTA can offer a convenient way to fight anaemia in a population, particularly in diets prevailing in developing countries (7).
According to the latest WHO estimations, 1.6 *billion* people suffer from this disorder (8).
After the first reports on the beneficial iron absorption characteristics of FeNa-EDTA, it took some 20 years before approval of this form of EDTA was achieved by JECFA in 1999 (9). However in the past decade good progress was made. A major break-through was in 2006 when the US FDA assigned the GRAS status (Generally Recognized As Safe) to FeNa-EDTA (10). In 2009 WHO started to recommend FeNa-EDTA as the preferred iron compound for the fortification of flour (11). Recently EFSA came out with a highly positive scientific opinion on FeNa-EDTA (12), resulting in an authorization by the European Commission to place FeNa-EDTA on the market in the entire EU (13). A recent review on the promise of a healthier iron status enabled by FeNa-EDTA was published in this journal (14).

acids so much more vulnerable for sensory deterioration than their omega-6 counterparts.

Combating radicals

Radicals can be combated in two ways: 1) by trapping them once they have been formed and 2) by preventing their formation. Most effectively both options are applied simultaneously (1). Many radical trapping agents comprise one or more phenol groups. Prevention is largely a matter of eliminating the activity of traces of iron and copper ions that are present in every food product. At levels even far below 1 ppm, these ions can readily catalyze the formation of a noticeable level of radicals.

Emulsions

salad dressings, combine water (metal ions) and lipids (PUFA's) in close vicinity to each other, these are especially at risk (28).

EDTA AND METAL-IONS

EDTA is a molecule that can hold metal ions, including of iron and copper, like a hand holding a tennis ball. In this way the ability of generating radicals is largely suppressed. No other food additive that can bind iron and copper ions to the same extent with respect to suppressing their propensity to generate radicals as can do EDTA (29). With respect to copper ions, it is worthwhile to mention that EDTA has been found very effective in mitigating the strong tendency of these metal ions to destroy ascorbic acid, when dissolved in water (30). Also iron-ions have been implicated to play major role in radical break-down reactions of PUFA's and also in these cases EDTA has been demonstrated in studies with synthetic micelles to strongly suppress this undesired reaction (31, 32).

DISODIUM EDTA AND CALCIUM EDTA

There are two different EDTA products that are allowed in food i.e. calcium disodium EDTA or short "calcium EDTA" ($CaNa_2$-EDTA) and "disodium EDTA" (Na_2H_2-EDTA). Neither in effectiveness nor with

these two forms.

When administered intravenously at high levels in test animals, Na_2H_2-EDTA has been found to be more toxic than $CaNa_2$-EDTA. This is because Na_2H_2

and subsequently starts to extract calcium ions from the endothelial cells lining the blood vessels. In case of $CaNa_2$-EDTA every EDTA molecule has its own calcium ion already, so there is never a need to extract one from a cell wall.

It should be emphasized that when added in the due low levels to food, this health risk is non-existent.

Unlike $CaNa_2$-EDTA, there are numerous technical (non-food) applications for Na_2H_2-EDTA. This poses a risk that non food-grade Na_2H_2-EDTA i.e. targeted for technical use material ends up in products earmarked for human consumption. As $CaNa_2$-EDTA is only used in food, the abovementioned food safety management risk of Na_2H_2-EDTA can be eliminated by not allowing its use in food, as is the case in the EU (see below).

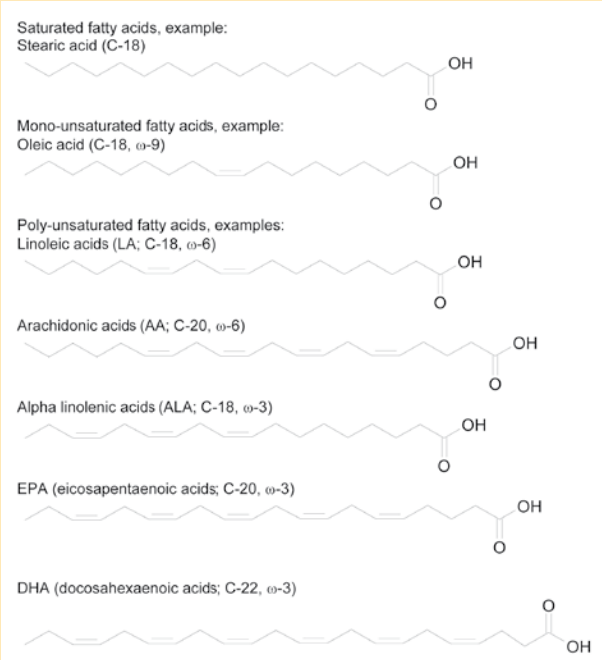
REGULATORY STATUS

After approval by the US FDA of both calcium EDTA and disodium

as well (33, 34), be it only for $CaNa_2$-EDTA and only for a much more limited number of products than allowed by the US FDA (35, 36). In the EU $CaNa_2$

385 (33). For a full overview of allowed uses in the EU and the USA of Ca_2Na_2-EDTA, see Tables 1and 2.

Figure 1. Chemical structures of fatty acids.



Starting at the "omega end" of the fatty acid chain, the first double bond can be positioned at the 3rd carbon atom (omega-3), the 6th carbon atom (omega-6) or the 9th carbon atom (omega-9, only in oleic acid) away from this last C atom.

Health benefits

One of the strongest advocates of the wide range of health benefits of omega-3 fatty acids from the global scientific community has been Dr. Artemis P. Simopoulos in the USA. Over two decades she has published quite a large number of highly worthwhile reviews on this subject (19, 20) underlining the importance of a correct intake *ratio* of omega-3 vs. omega-6 fatty acids. To-date this ratio is believed to be too much biased towards the omega-6's. Apparently this disturbance in our diet is an unintentional heritage of the Industrial Revolution two centuries ago.

In a recent interview, that happens to pop up as the first hit of a "GOOGLE search" on her name (21), she explains: "When the proper amount of omega-3 fatty acids are not consumed, people are at much greater risk for most of the major killer diseases afflicting humankind today, including heart attack, stroke, cancer, obesity, insulin resistance, diabetes, asthma, arthritis, lupus, and even depression".

Recently further evidence for a link between obesity and omega-3 deficiency was revealed (22).

Admittedly a trivial argument, but it is remarkable to note that a dihydroxy derivative of DHA (acting as a cell messenger) has been baptized in literature simply as "neuroprotectin", underlining its protective effect in nerve cells (23).

There are also some question marks left over with respect to health effects of omega-3's e.g. the usefulness of fortifying infant formulas with DHA (24).

PUFA's extremely sensitive to radical attack. On one hand this is beneficial, allowing an easy conversion in the cell membranes to signal molecules like neuroprotectin, on the hand it renders them highly vulnerable to harmful oxidative damage (25).

For sure there is still a plenty of room for more worthwhile and interesting research in this fascinating area of health science.

Market trend

All these many years of scientific work and promotional activities have not failed to leave behind a clear result: The awareness amongst consumers about the health effects of "omega-3's" has increased significantly. This is reflected by a rise of the commercial availability of food products enriched in omega-3 fatty acids, particularly of the long-chain ones i.e. EPA and DHA.

Anti-oxidants and Radicals

Among consumers there is also a wide-spread notion of a link between "anti-oxidants" and health benefits. The primary role of anti-oxidants is to eliminate the detrimental effects of a class of highly reactive chemical compounds called "radicals". Various parts of living systems can be damaged by radicals and Life itself may even be regarded as a continuous fight against the adverse impact of radicals (25).

Not only in living systems can radicals do a lot of harm, also in food products radicals often adversely affect sensory properties, resulting in a shorter shelf life. This is the reason why many food products contain anti-oxidants in order to minimize the level of deterioration caused by radicals. These anti-oxidants are also known as shelf-life enhancing agents.

Radicals and PUFA's

One of the components in both food ingredients and living systems that are most easily attacked or "oxidized" by radicals are PUFA's. It is the CH2 group just in between two double bonds (CH=CH-$CH_{2\text{-CH=CH})}$ that is extremely vulnerable. Attack by radicals of these PUFA's results in the formation of volatile compounds such as aldehydes, ketones and alcohols, all characterized by a rancid and repugnant odour and taste.

Odour and taste defects

A detailed overview about these fatty acid break-down products and their possible mechanisms of formation is given by Belitz, Grosch and Schieberle (26).

Most remarkable is that some of these break-down products possess an extremely low odour threshold (far less than 1 ppb) such as trans-4,5-epxoy-trans-decen-2-al and 1,5-cis-octadien-3-one.

As a highly informative illustration of a full investigation towards taste defects due to fatty acids has been described in a PhD thesis of Wageningen University relating to work conducted at the Netherlands Institute for Dairy Research (NIZO) on cold-stored butter (27). Although dating from before the health benefits of omega-3 had become apparent at all, the presence of omega-3 alpha-linolenic acid (ALA) was particularly believed to be the major contributor to the observed taste defects.

In this study copper ions, rather than iron or manganese ones, were thought to be the major culprit.

One can speculate whether it is the very formation of 1,5-cis-octadien-3-one, which can only be formed starting from omega-3 fatty acids, that renders this latter class of fatty

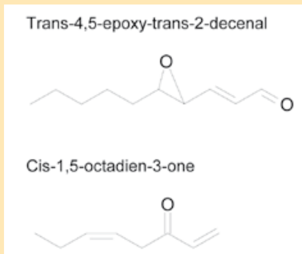


Figure 2. Two examples of volatile PUFA break-down products with an extremely low odour threshold.

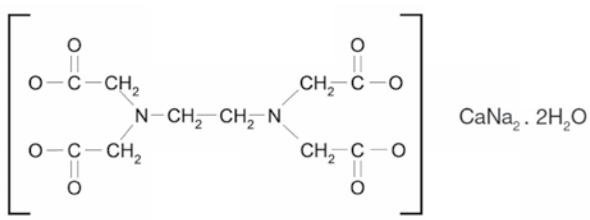


Figure 3. Structural formula of calcium disodium EDTA ($CaNa_2$-EDTA).

EDTA in the environment

EDTA is a synthetic chemical with a wide range of applications, all targeted at controlling solubility and reactivity of metal ions. It is rather inert to living systems. In the human body EDTA is not metabolized at all and rapidly excreted by the kidneys. EDTA is not affected in sewage treatment plants that are run at the standard pH value of 5. Remarkably, at a pH value of 8, EDTA has been found to be readily biodegradable (15). This means that under these conditions it is rapidly degraded by microorganisms. When complexed to a ferric ion, EDTA is rapidly broken down too, not by microorganisms, but by sunlight. Therefore, in the environment biodegradation of EDTA proceeds only slowly but eventually it is fully broken down and hence cannot be classified persistent. Its environmental behaviour is therefore referred to as "inherently biodegradable" (16).

In many industrial applications EDTA is being replaced now by alternatives with a faster biodegradability profile that does meet current international standards for the desired classification as readily biodegradable (6).

Note that in food the volumes of EDTA are low compared to most other uses e.g. in cleaning applications.

Safety of EDTA

The inertness of EDTA molecules to living systems is reflected by their total absence of toxicity. As practiced in chelation therapy, EDTA can be administered intravenously into humans up to gram amounts without any adverse health effect. Chelation therapy is widely practiced nowadays. Whether this practice can reverse atherosclerosis is still being disputed, but for lead poisoning it is well accepted as a medical treatment (17). Numerous extensive animal trials and decades of use by humans have demonstrated that EDTA is chemical compound with extremely high level of safety with respect to human consumption when used at the recommended intake levels (18).

Fatty acids

One category of basic food components are lipids. Major building blocks of lipids are fatty acids. Depending on their chemical structure, they can be classified as saturated, mono-unsaturated or poly-unsaturated. In saturated fatty acids no double C=C bond is present, in mono-unsaturated ones only one and in poly-unsaturated fatty acids (PUFA's) two or more. PUFA's on their turn can be of the type omega-6 or omega-3.

Omega-3's

In Figure 1 an overview is given of the most common fatty acids. Most fatty acids contain 18 carbon atoms. In case of PUFA's also fatty acids with a chain length of 20 and 22 C-atoms play an essential role. These can be synthesized starting from of their C-18 predecessors via two biochemical processes called elongation and desaturation. However in the human body this conversion process is not always effective while the omega number of a fatty acid chain can never be altered. The C-18 omega-6 fatty acid linoleic acid (LA) can be only converted to the C-20 analogue arachidonic acid (AA), and the C-18 omega-3 fatty acid alpha-linolenic acid (ALA) only to the long-chain omega-3's EPA (eicosapentaenoic acid; C-20) and DHA (docosahexaenoic acid; C-22).

With a daily intake of too much LA (C-18 omega-6) and too little ALA (C-18 omega-3) this process of elongation and desaturation results in the formation of too much AA and too little EPA and DHA with all the adverse effects on health that go with it.

E 385	Calcium disodium ethylene diamine tetra-acetate (Calcium disodium EDTA)	Emulsified sauces	75 mg/kg
		Canned and bottled pulses, legumes, mushrooms and artichokes	250 mg/kg
		Canned and bottled crustaceans and molluscs	75 mg/kg
		Canned and bottled fish	75 mg/kg
		Spreadable fats as defined in Annexes B and C to Regulation (EC) No 2991/94 (*), having a fat content of 41 % or less	100 mg/kg
		Frozen and deep-frozen crustaceans	75 mg/kg
		Libamáj, egészben és tömbben	250 mg/kg

Table 1. $CaNa_2$-EDTA as currently allowed for food use in the EU (38).

Food	Limitation (ppm)
Cabbage, pickled	220
Canned carbonated soft drinks	33
Canned white potatoes	110
Clams (cooked canned)	340
Crabmeat (cooked canned)	275
Cucumbers pickled	220
Distilled alcoholic beverages	25
Dressings, nonstandardized	75
Dried lima beans (cooked canned)	310
Egg product that is hard-cooked and consists, in a cylindrical shape, of egg white with an inner core of egg yolk	200
Fermented malt beverages	25
French dressing	75
Legumes (all cooked canned, other than dried lima beans, pink beans, and red beans)	365
Mayonnaise	75
Mushrooms (cooked canned)	200
Oleomargarine	75
Pecan pie filling	100
Pink beans (cooked canned)	165
Potato salad	100
Processed dry pinto beans	800
Red beans (cooked canned)	165
Salad dressing	75
Sandwich spread	100
Sauces	75
Shrimp (cooked canned)	250
Spice extractives in soluble carriers	60
Spreads, artificially colored and lemon-flavored or orange-flavored	100

Table 2. $CaNa_2$-EDTA as currently allowed for food use by the US FDA (36).

For all food additives, including EDTA, a maximum ADI (Acceptable Daily Intake) is applicable. (37). There is a concern is that with too many food products being stabilized with EDTA, this maximum ADI could be exceeded (18). Hence, adding a new food item to the approved list is not a straightforward procedure. In 2006 the Hungarians (EU Member State since 2004) succeeded in obtaining approval for adding EDTA to their national delicatessen "libamáj" (liver paté) (38).

OUTLOOK FOR THE FUTURE

From a toxicological point of view there is certainly room to expand the use of EDTA in food. Based on the absence of any indication for toxicity of EDTA via oral intake, a rise of the maximum ADI could be considered. Alternatively the currently permitted use of EDTA in the EU as a stabilizing agent in "emulsified sauces" and in "spreadable fats [...] having a fat content of 41 percent or less" could be extended to all food products consisting out of emulsions of lipids in water. Such a decision could pave the way for a healthier diet based on a more balanced intake of omega-3 fatty acids.

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