IN PARTNERSHIP WITH JUNGBUNZLAUER,
C&EN PRESENTS

c&en | WHITE PAPERS

A Highly Bioavailable Zinc Source in Support of Human Health

BROUGHT TO YOU BY

Jungbunzlauer

From nature to ingredients®

Jungbunzlauer

From nature to ingredients®

facts

A highly bioavailable zinc source in support of human health

Abstract

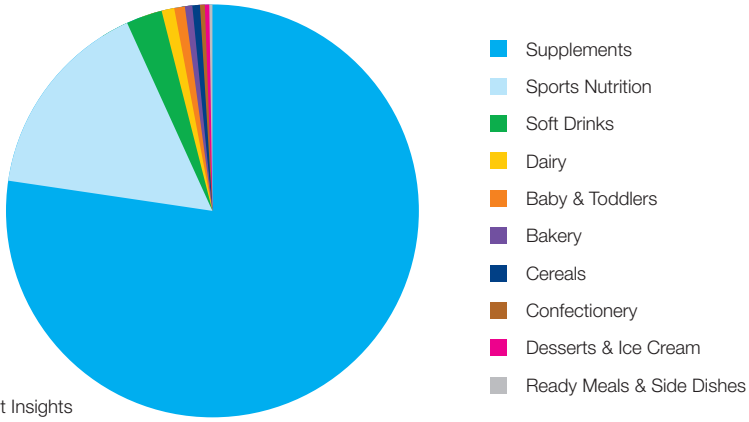
Growing interest in global health has manufacturers looking at minerals in a new light. Zinc citrate is a great solution for formulation and supplementation due to its high bioavailability, high zinc content (31%) and preferred sensory properties. Multiple forms of zinc are approved for use in food and dietary supplements, but many of them have drawbacks regarding taste and bioavailability.

Innova Marketing Insights shows the number of product launches in the supplement and food industry containing zinc grew at 11% annually over the last five years. Interestingly, zinc citrate exceeded this number with 18% annually. Higher growth rate for zinc citrate may be a result of consumers' growing interest in health, bioavailability and zinc citrate's benefits in formulation.

The supplement category held the largest number of launches when comparing the top 10 product launch categories for both zinc and zinc citrate. Over 76% of zinc citrate's launches were in the supplement category when comparing the top 10 product launch categories, opposed to zinc's 32%. Over the last 5 years, zinc citrate saw increased use in novel dosage formats like gummies and powders, potentially due to the high zinc content and superior taste profile (Innova Market Insights Data).

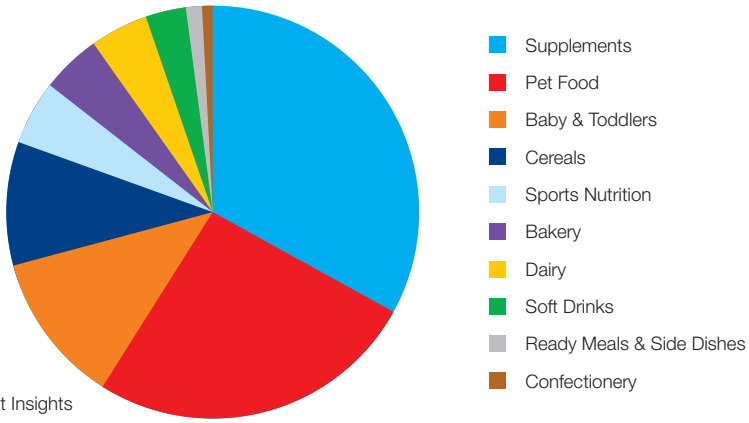
Charts from Innova Market Insights below show top 10 categories of global product launches of zinc vs zinc citrate in 2015 – August 2020.

Chart 1: Global Zinc Citrate Launches 2015 – August 2020



Source:
Innova Market Insights

Chart 2: Global Zinc Launches 2015 – August 2020



Source:
Innova Market Insights

This paper discusses important nutritional and technical aspects of zinc fortification. It provides guidance for the use of zinc in fortified foods and supplements and the results of a bioavailability study with zinc citrate.

Introduction

Zinc has taken the spotlight as a key ingredient in health focused formulations as it supports normal functions of the immune system; zinc ions are involved in regulating intracellular signalling pathways for innate and adaptive immune cells.

Zinc is commonly recognized for its link to the immune system, but also serves other critical roles in maintaining human health. In 1963, Prasad and his co-workers first documented zinc's importance in human health[1] and since then, the importance of zinc in our body and numerous health benefits have been widely recognized. Zinc supports protein and DNA synthesis, enzyme function, bone structure, nerve function and cognitive function[1].
Zinc is an essential mineral, which is a component of approximately 300 enzymes and 2000 transcriptional factors[2-5]. About 10% of the human proteome contain zinc-binding motives.

The European health claims regulation, which is seen as the most respected and comprehensive evaluation of global health claims, highlights the importance of zinc for human health. Zinc received more positive opinions than any other mineral. See the range of claims approved (table 1). The respective dossiers can be used by other authorities as well and potentially influence other regions in the world.

Table 1: Authorised health claims in the EU according to Art. 13.1 health claims list of Regulation (EC) No 1924/2006

Normal function of the immune system
Normal DNA synthesis
Role in the process of cell division
Protection of cells from oxidative stress
Maintenance of normal bones
Normal cognitive function
Normal fertility and reproduction
Normal macronutrient and carbohydrate metabolism
Normal acid-base metabolism
Normal metabolism of vitamin A
Normal metabolism of fatty acids
Maintenance of normal vision
Maintenance of normal skin
Maintenance of normal hair
Maintenance of normal nails
Normal protein synthesis
Maintenance of normal testosterone levels in blood

Good dietary sources for zinc are primarily foods of animal origin, like, meat, liver, fish, milk and cheese. Zinc plant sources, like legumes and whole grains, are often less bioavailable because of potential intestinal absorption impairment by anti-nutritive factors like phytic acid[6]. Inadequate intake of zinc in the diet and lack of absorption of zinc are the predominant causes of zinc deficiency, but zinc can also be lost due to diarrhoea[7-8].

The global prevalence of zinc deficiency was estimated at 31%, ranging from 4-73% across sub-regions. Based on these estimates, zinc deficiency in children aged below five years was estimated to cause 176,000 diarrhoea deaths, 406,000 pneumonia deaths and 207,000 malaria deaths per year[9]. Zinc deficiency is rather uncommon in populations with predominantly Western style nutrition because of the high proportion of animal products and particularly meat in the diet.

Zinc bioavailability is of critical importance to prevent deficiencies for those at higher risk, in particular plant-based eaters and populations who may have trouble utilizing and absorbing zinc, for example elderly people and individuals in which gastric dysfunctions (e.g. gastric atrophy and achlorhydria)[10-11].

The recommended daily allowance (RDA) set by the Food and Drug Administration (FDA) for zinc recommends that women aged 19 and up get 8 milligrams (mg) of zinc per day (that increases to 11 mg for pregnant and 12 mg for lactating women) while men should get 11 mg per day. The RDA for zinc in the EU is 10 mg. The Codex Alimentarius International Food Standard nutrient reference value (NRV) recommends 11-14 mg of zinc depending on your diet.

Characteristics of zinc compounds

A wide variety of zinc salts are available for use in functional foods, dietary supplements and drug products. The most common forms are zinc oxide, zinc sulfate and zinc gluconate, the latter two (together with zinc acetate) are recommended by the WHO for use in syrups or dispersible tablets for diarrhoea treatment in infants[12].

Only small amounts of zinc are typically needed for formulations, however, there is a wide variation in mineral content, solubility and taste from different sources (table 2) which impacts the dosage of the specific zinc form and overall cost of the formulation. When considering applications with limited space, like multi-vitamins, compounds with high zinc content may be particularly beneficial.

Table 2: Commonly used zinc salts approved for fortification in the EU according to Regulation (EC) No. 1825/2006

Compound	Mineral Content	Solubility	Taste
Zinc Citrate·3 H_2O	31%	3 g/l	Slightly bitter
Zinc Gluconate·xH_2O	13%	100 g/l	Bitter, astringent
Zinc Oxide	80%	Insoluble	Bitter
Zinc Sulphate·7 H_2O	23%	960 g/l	Astringent, bitter, metallic
Zinc Lactate	23%	55 g/l	Slightly bitter, astringent

Highly soluble salts like zinc sulphate, zinc gluconate and zinc acetate have a strong metallic, bitter and astringent taste that often need to be masked, plus their high reactivity may lead to unwanted side-reactions in the formula. Even at the typically low dosage levels of zinc salts in fortified foods, off tastes can be noticeable. Particularly in the case of food supplements or drug products like syrups and oral dispersible or effervescent tablets, off tastes can limit the dosage level of these compounds. However, better tasting zinc oxide is insoluble and existing data indicates that its bioavailability is at the lower end of available zinc compounds. In contrast to the oxide form, zinc gluconate stands out for its high bioavailability, but its low zinc content makes this compound much more expensive. An alternative zinc salt with promising sensory and formulation properties is zinc citrate. This compound has a high zinc content of 31%, is slightly soluble in water, has low reactivity, is odourless, and has relatively low costs[13].

Trials at the Jungbunzlauer Application Technology Centre show that the addition of tripotassium citrate or trisodium citrate increase solubility. Zinc citrate, or a combination of zinc citrate and tripotassium citrate result in significantly less bitter composition when compared to other soluble zinc sources like zinc sulfate or zinc sulfate or zinc gluconate (table 3).

Table 3: Taste ranking test for bitterness for solutions containing 10 mg Zn^{2+} per 5 ml each; (Rank: 1= least pronounced bitterness). Values that do not share a common letter are significantly different ($p<0.05$)

	Zinc Citrate (dispersed)	Zinc Citrate (dissolved w. tripotassium citrate)	Zinc Sulfate	Zinc Gluconate
Average rank	1.8^{A}	1.6^{A}	3.1^{B}	3.8^{B}

Zinc sulfate and zinc gluconate have further been described as having a strong metallic and astringent taste (Source: Internal tasting panel (n=10) at Jungbunzlauer Ladenburg GmbH, Germany)

Bioavailability of zinc salts

Intestinal absorption of zinc and adequate utilisation by the body – in other words, the bioavailability – depends on several factors, such as the chemical form of the zinc salts, dietary factors and physiological condition (table 4).

Table 4: Factors affecting bioavailability of zinc

Chemical form of zinc salts	Dietary factors	Physiological conditions
Solubility	Amount/concentration of zinc	Zinc status and foregoing zinc supply / depletion
Complexing /chelating anions	Inhibiting factors (phytic acid)	Gastric acid, luminal pH
	Promoting factors (protein, certain amino acids, citric acid)	Particular requirements (growth, gravidity, lactation, old age)
	Fe-Zn/Zn-Cu interactions	Dietary status/eating habits (malnutrition, vegetarianism)
		Increased needs due to diseases such as diarrhoea

It is demonstrated in animal and human trials that absorbability is strongly related to the specific solubility of zinc compounds in aqueous solution. Therefore, acidic inorganic zinc salts like zinc chloride or zinc sulfate, which are very soluble in aqueous solution, show sufficient bioavailability, whereas zinc absorption from the oxide or carbonate salt, which are practically insoluble in neutral aqueous solution, is significantly lower[14-16]. Zinc salts with organic anions (zinc acetate, zinc lactate) and particularly with amino acid chelates like zinc histidine[17] and other reversibly complexing anions (e.g., zinc gluconate[18] or zinc citrate) are thought to have a generally higher bioavailability than zinc sulfate. However, human absorption data to support the usage of zinc citrate has so far been very limited.

From the published data on the absorption of zinc from supplements given to humans, it would appear that zinc gluconate, zinc citrate, and zinc sulfate are absorbed at a similar level, while zinc oxide is slightly less well absorbed[19-20].

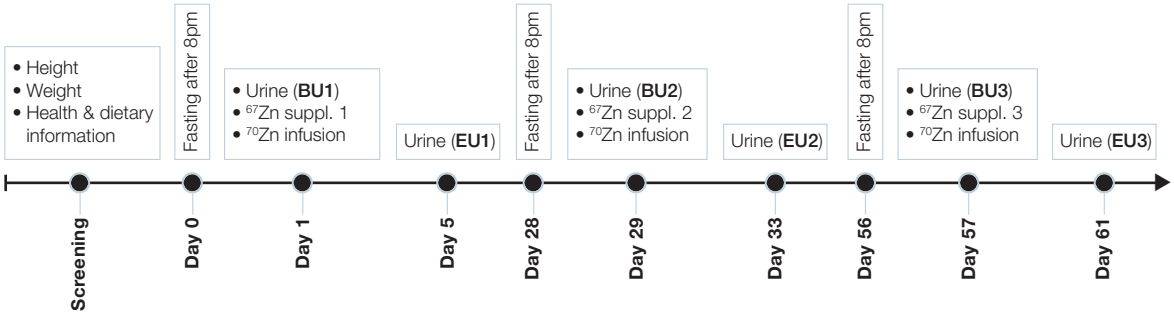
Bioavailability study

The ETH Zurich, Switzerland, studied the bioavailability of two assumed high bioavailable salts (zinc citrate and zinc gluconate) with the supposed lower bioavailable zinc oxide[13]. The goal of this study was to use the double-isotope tracer ratio (DITR) method[21-23] to compare the absorption of these three compounds when they were given as supplements without food. This procedure is recommended to maximize zinc absorption and is usually advised for compounds targeted for the treatment of diarrhoea. The isotope tracer technique which was used included the administration of two stable zinc isotopes (one orally and one intravenously), followed by the quantification of the two isotopes in one spot urine sample four days later.

Fifteen adults were included in this randomised, double masked, 3-way crossover study, meaning each participant acting as his/her own control (figure 1). Healthy male and female participants aged between 18 and 45 years were selected, who were not vegan, smokers, pregnant, or lactating.

Zinc gluconate, zinc oxide, and zinc citrate were administered as supplements at a dose of 10 mg of zinc each and consumed with water. Each dose consisted of 9 mg of non-labelled and 1 mg of ^{67}Zn-labelled zinc. Additionally, ^{70}Zn-labelled $ZnCl_2$ was used for intravenous administration.

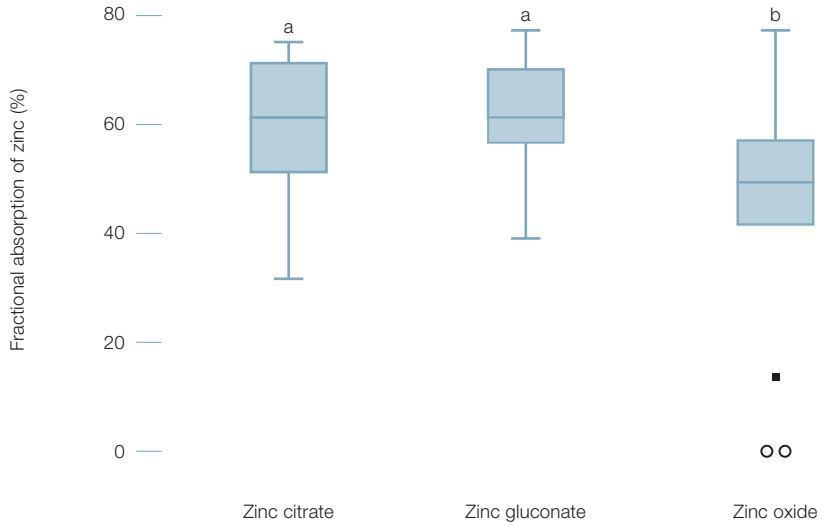
Figure 1: Detailed study procedure (the 3 different test supplements were administered in random order)



BU: baseline urine; EU: enriched urine. (With kind permission of R. Wegmüller)

The study showed that there was a significantly higher absorption of zinc from zinc citrate (median absorption 61.3%; *P* = 0.006) and zinc gluconate (median absorption 60.9%; *P* = 0.009) when compared with the one from zinc oxide (median absorption 49.9%), see figure 2. The absorption of zinc citrate did not significantly differ from that of zinc gluconate.

Figure 2: Fractional absorption of zinc from zinc citrate, zinc gluconate, and zinc oxide supplements (n = 15)



(With kind permission of R. Wegmüller)

Another interesting finding was that two (one male, one female) of the 15 participants did not absorb zinc from zinc oxide and one further participant absorbed the zinc oxide at a low level (14%). This suggests that there is a portion of the population that is not able to absorb zinc in the oxide form. It was hypothesised that these individuals cannot dissolve zinc oxide in the gastric juice, probably as a result of a less acidic intragastric pH making it poorly absorbable.

These results indicate that zinc citrate can be a useful compound for zinc supplementation. At the present time, the WHO recommends the use of the highly- soluble compounds zinc sulfate, zinc acetate or zinc gluconate in the form of syrups or dispersible tablets in the management of diarrhoea[12]. Zinc citrate might be a useful addition to this list and be especially suitable for chewable/crushable tablets because it has better sensory properties than zinc acetate, zinc sulfate[24], and zinc gluconate, which has an astringent, bitter, or metallic taste. In relation to price and zinc content, zinc citrate would have an advantage over zinc gluconate due to its higher zinc content (31% vs 13%). The advantage of zinc citrate over zinc sulfate is related to its better sensory qualities and the higher zinc content of citrate (31% vs 23%) at a similar price and presumably for a similarly high absorption[25].

Summary

Awareness of zinc and its many health benefits continues to increase. Its physiological versatility, which offers options for new product concepts, combined with its relative low cost in use, demonstrates why zinc and particularly zinc citrate is forecasted for additional growth within fortified foods and supplements.

While a number of zinc salts are approved for the usage in food and food supplements, many of them have drawbacks regarding taste, which limit their usage in taste sensitive applications or require extensive work for masking them. Commonly used zinc oxide combines a relative low taste impact at a very low price. The assumed lower bioavailability was recently confirmed and the fact that some individuals can only absorb it minimally questions its general usage for zinc fortification or supplementation.

Zinc citrate combines formulation advantages like preferred sensory properties, relatively low costs in use due to a high zinc content of 31% as well as sufficient solubility. Combined with the recently proven high bioavailability similar to zinc gluconate, this makes zinc citrate a serious option for zinc fortified foods and zinc supplements.
Zinc Citrate is part of Jungbunzlauer's Special Salts group, which are functional minerals mainly derived from non-GMO citric acid, gluconic acid or lactic acid. The fully reacted products are manufactured in Europe by neutralisation of these acids with the appropriate alkaline calcium, magnesium, potassium and zinc sources. The resulting organic minerals are known for their high bioavailability, and are used because of their ability to support human health in different applications of food, beverage, dietary supplements or pharmaceutical products.

References

[1] Prasad, A.S., Miale, A., Farid, Z., Sandstead, H.H., Schulert, A.R. (1963) Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypognadism. J. Lab. Clin. Med. 61, 537–549.

[2] Coleman JE. (1992) Zinc proteins: enzymes, storage proteins, transcription factors, and replication proteins Annu Rev Biochem. 61:897–946.

[3] Vallee, B.L., Falchuk, K.H. (1993) The biochemical basis of zinc physiology. Physiol. Rev. 73, 79– 118.

[4] SCF. (1992) Directorate-General International Market and Industrial Affairs: Reports of the Scientific Committee for Food. Nutrient and Energy Intakes for the European Community. Thirty-first series.

[5] Cai, L., Li, X. K., Song, Y., & Cherian, M. G. (2005) Essentiality, Toxicology and Chelation Therapy of Zinc and Copper. Current Medicinal Chemistry, 12(23): 2753–2763.

[6] FAO/WHO. (2002) Human Vitamin and Mineral Requirements. Report of a Joint FAO/WHO Expert Consultation Bangkok, Thailand. FAO.

[7] Gibson RS (1994) Zinc nutrition in developing countries. Nutrition Research Reviews, 7:151–173.

[8] WHO (1996) Zinc. In: Trace elements in human nutrition and health. World Health Organization, Geneva.

[9] Caulfield, L, Black, R. (2004) Zinc deficiency. In Ezzati et al. (ed.) Comparative Quantification of Health Risks, Volume 2, World Health Organization.

[10] Henderson LM, Brewer GJ, Dressman JB, Swidan SZ, DuRoss DJ, Adair CH et al. (1995) Effect of intragastric pH on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. J Parenter Enteral Nutr 1995;19:393–7.

[11] Wong CP, Magnusson KR, Ho E. (2013) Increased inflammatory response in aged mice is associated with age-related zinc deficiency and zinc transporter dysregulation. J Nutr Biochem. 2013 Jan; 24(1):353–9.

[12] WHO. (2007) Production of Zinc Tablets and Zinc Oral Solutions, Guidelines for Programme Managers and Pharmaceutical Manufacturers.

[13] Wegmüller et al. (2014) Zinc Absorption by Young Adults from Supplemental Zinc Citrate Is omparable with That from Zinc Gluconate and Higher than from Zinc Oxide. J. Nutr. 144: 132–136, 2014.

[14] Budavari S, ed. (1989) The Merck index: an encyclopaedia of chemicals, drugs and biologicals. 11th ed. Rahway, NJ: Merck and Co.

[15] Oelshlegel FJ, Brewer GJ. (1977) Absorption of pharmacologic doses of zinc. In: Brewer GJ, Prasad AS, eds. Zinc metabolism: current aspects in health and disease. Vol 14. New York: Alan R Liss, 1977:299–316.

[16] Prasad AS, Beck FWJ, Nowak J. (1993) Comparison of absorption of five zinc preparations in humans using oral zinc tolerance test. J Trace Elem Exp Med;6:109–15.

[17] Schölmerich J, Freudemann A, Köttgen E, Wietholtz H, Steiert B, Löhle E, Häussinger D, Gerok W. (1987) Bioavailability of zinc from zinc-histidine complexes. I Comparison with zinc sulfate in healthy men. Am J Clin Nutr 45: 1480–1486.

[18] Neve J, Hanocq M, Peretz A, Khalil FA, Pelen F. (1992) Absorption and metabolism of oral zinc gluconate in humans in fasting state, during, and after a meal. Biol Trace Elem Res 32: 201–212.

[19] Siepmann M, Spank S, Kluge A, Schappach A, Kirch W. (2005) The pharmacokinetics of zinc from zinc gluconate: a comparison with zinc oxide in healthy men. Int J Clin Pharmacol Ther.;43:562–5.

[20] Wolfe SA, Gibson RS, Gadowsky SL, O'Connor DL. (1994) Zinc status of a group of pregnant adolescents at 36 weeks gestation living in southern Ontario. J Am Coll Nutr.;13:154–64.

[21] Guillem A, Alegria A, Barbera R, Farre R, Lagarda MJ, Clemente G.(2000) In vitro dialyzability of zinc from different salts used in the supplementation of infant formulas. Biol Trace Elem Res.;75:11–19.

[22] Friel JK, Naake VL Jr, Miller LV, Fennessey PV, Hambidge KM. (1992) The analysis of stable isotopes in urine to determine the fractional absorption of zinc. Am J Clin Nutr.;55:473–7.

[23] Lowe NM, Woodhouse LR, Matel JS, King JC. (2000) Comparison of estimates of zinc absorption in humans by using 4 stable isotopic tracer methods and compartmental analysis. Am J Clin Nutr.;71:523–9.

[24] Brown KH, Rivera JA, Bhutta Z, Gibson RS, King JC, Lönnerdal B, Ruel MT, Sandtröm B, Wasantwisut E, Hotz C, International Zinc Nutrition Consultative Group (IZiNCG). (2004) Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull.;25:S99–S203.

[25] Tran CD, Miller LV, Krebs NF, Lei S, Hambidge KM. (2004) Zinc absorption as a function of the dose of zinc sulfate in aqueous solution. Am J Clin Nutr.;80:1570–3.

About Jungbunzlauer

Jungbunzlauer is one of the world's leading producers of biodegradable ingredients of natural origin. We enable our customers to manufacture healthier, safer, tastier and more sustainable products. Thanks to continuous investment, state-of-the-art manufacturing processes and comprehensive quality management, we are able to provide outstanding product quality.

Our mission "From nature to ingredients®" commits us to protecting people and their environment.

The Authors

Markus Gerhart – Director of AGC, Jungbunzlauer Ladenburg GmbH
markus.gerhart@jungbunzlauer.com

Monica Garces – Market Development Manager Health & Nutrition, Jungbunzlauer Inc.
monica.garces@jungbunzlauer.com

Danielle Wedral Licata – Market Development Manager Health & Nutrition, Jungbunzlauer Inc.
danielle.wedral-licata@jungbunzlauer.com

Discover more on
www.jungbunzlauer.com

Headquarters **Jungbunzlauer Suisse AG**
4002 Basel · Switzerland · Phone +41 61 295 51 00 · headquarters@jungbunzlauer.com · www.jungbunzlauer.com