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REVIEW ARTICLE

Thirteen decades of antimicrobial copper compounds applied in agriculture. A review

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Abstract

Since the initial use of Bordeaux mixture in 1885 for plant disease control, a large number of copper-based antimicrobial compounds (CBACs) have been developed and applied for crop protection. While these compounds have revolutionized crop protection in the twentieth century, their continuous and frequent use has also raised concerns about the long-term sustainability of copper (Cu)-based crop protection system. Here, we review CBACs used in crop protection and highlight their benefits and risks, and potential for their improvement and opportunities for further research to develop alternatives to CBACs. The major findings are (i) the relatively high toxicity to plant pathogens, low cost, low mammalian toxicity of the fixed Cu compounds, and their chemical stability and prolonged residual effects are major benefits of these compounds; (ii) phytotoxicity, development of copper-resistant strains, soil accumulation, and negative effects on soil biota as well as on food quality parameters are key disadvantages of CBACs; (iii) regulatory pressure in agriculture worldwide to limit the use of CBACs has led to several restrictions, including that imposed by the regulation 473/2002 in the European Union; and (iv) mitigation strategies to limit the negative effects of CBACs include their optimized use, soil remediation, and development and application of alternatives to CBACs for a sustainable crop protection. We conclude that recent research and policy efforts have led to the development of a number of alternatives to CBACs, which should be further intensified to ensure that growers have sufficient tools for the implementation of sustainable crop protection strategies.

Keywords Chemical control · Copper compounds · Crop protection · Organic farming · Pathogen resistance development · Phytotoxicity · Soil accumulation · Sustainable agriculture

Contents

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1 Introduction

The first copper-based antimicrobial compound (CBAC) used in agriculture was Bordeaux mixture (copper sulfate pentahydrate and lime mixture), which was accidentally discovered in 1885 by the French scientist Pierre-Marie Alexis Millardet (Gayon and Sauvageau 1903). At the time, Millardet noticed that vines which were daubed with this mixture, by French growers in the Bordeaux region, to make the grapes unattractive to passers-by and animals, were free of downy mildew, one of the most economically important diseases caused by *Plasmopara viticola*. This led him to perform experiments which finally confirmed that this mixture could effectively control the mildew disease at a very low cost. By then, the Bordeaux mixture was the first copper (Cu) fungicide to be used on a large scale worldwide. The antifungal properties of copper sulfate for treatment of wheat seeds against smut spores and preservation of wood were, however, already known even before the discovery of the Bordeaux mixture (Johnson 1935). Nevertheless, due to the high solubility in water and penetration capacity of copper ions in actively growing plant tissues, copper sulfate was highly phytotoxic and unsuitable for protective applications on foliage and fruit. During the preparation of the Bordeaux mixture, the reaction of calcium hydroxide with copper sulfate results in the formation of a colloidal blue suspension of copper hydroxide, practically insoluble in water, stabilized by the adsorption of calcium sulfate. In the fixed or complexed form, copper is not absorbed by the plant tissue, which reduces the risk of phytotoxicity of the Bordeaux mixture and increases the utility of copper sulfate in agriculture.

Following the use of Bordeaux mixture as a fungicide, there was a rapid development of CBACs, which has revolutionized the twentieth century agriculture in general, and crop protection in particular. The relatively high toxicity to plant pathogens, low cost, low mammalian toxicity of the fixed Cu compounds, and the chemical stability, which prevent them from being readily washed from plant surfaces and long residual periods, are among the most important advantages of these compounds (Cha and Cooksey 1991). This has led to the widespread use of Cu to control foliar plant pathogens with satisfactory levels of disease management. Consequently, CBACs have become an important component of integrated pest management (IPM) system seeking to provide long-term solutions for disease management. In the framework of IPM, CBACs are combined with resistant or tolerant cultivars, cultural, physical, and even biological control methods. CBACs are widely used both for control of bacterial diseases affecting crops as well as against a number of fungi and oomycetes. In organic farming, CBACs are the most effective active ingredients against a number of pathogens such as anthracnose, downy mildew of grapevine, late blight of potato and powdery mildew of many other crops (Finckh et al. 2015).

Copper compounds are strictly used as protectants as they have no curative or systemic activity, meaning that disease management is improved as they reduce inoculum buildup on susceptible leaf tissues preventing infection. Because Cu ions are released slowly, fixed Cu is less phytotoxic to plants and provide a better residual activity against diseases than can be achieved with non-fixed Cu. On plants, fixed Cu is predominantly insoluble (Menkissoglu and Lindow 1991) and once applied, Cu particles may or may not adhere to leaf surfaces (Fig. 1), to provide a protective film. Such a film acts as a reservoir that upon contact with water and low pH slowly releases Cu ions that are toxic to microbial cells. The concentration of Cu ions on leaves depends on the equilibrium established with the complexed and soluble forms of Cu (Menkissoglu and Lindow 1991). Exudates from the plant and microorganisms also play an important role

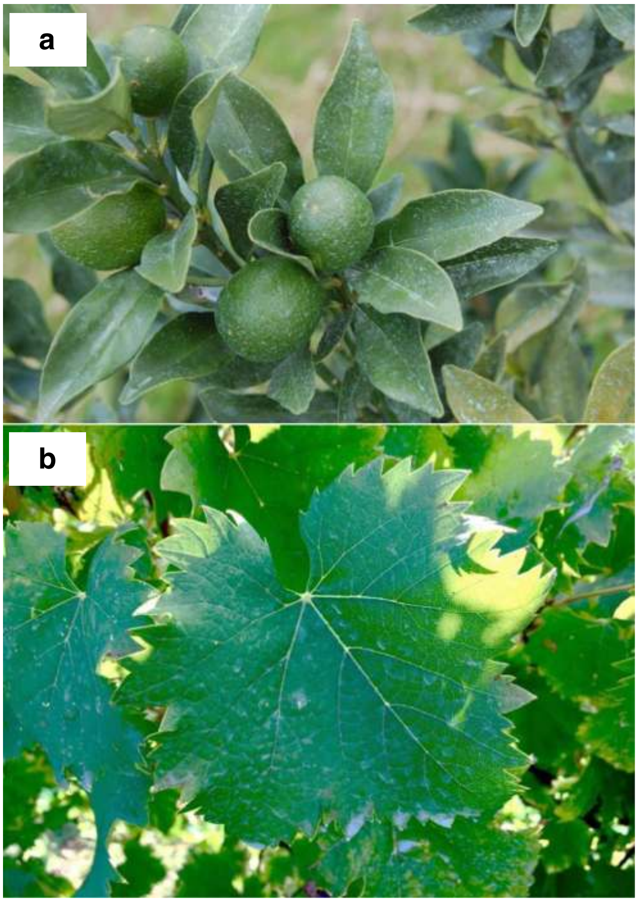

Fig. 1 Adherence of copper-based antimicrobial compounds after spray on leaf and fruit surfaces of citrus tree (**a**) and grapevine leaf (**b**) which provide a protective barrier against plant pathogens. The level of adherence of these compounds on plant surfaces depends on a number of factors including the type of leaf surface (smooth versus rough) and weather conditions

in Cu solubility by forming weak acids that lower the pH of the water on the plant surface, which increases Cu solubility and availability (Arman and Wain 1958). In addition, differences in the structural characteristics of plants—including stomatal density, cuticle layer thickness, and epidermal hairs density—affect the absorption of Cu ions by leaf surfaces (Fu et al. 2015).

There are concerns that frequent applications of CBACs have led to the emergence of copper-resistant strains in agriculture raising doubt on the long-term sustainability of agricultural production. In addition, CBACs have adverse effects on the environment and biodiversity, such as contamination of soil and groundwater, with significant impact on soil biota (Kandeler et al. 1996; Merrington et al. 2002). Furthermore, soil accumulation is likely to affect crop health in the long term. Ionic Cu, which is the toxic form to plants and microorganisms, is bound in the soil to particles of organic matter, clay, and metal hydroxides. Hence, downward movement of Cu through the soil profile is greater in sandy soils than soils rich in clay or organic matter (Alva et al. 1995). Moreover, Cu availability and toxicity in the soil is prominently increased as the soil pH decreases. At higher pH, Cu remains in insoluble forms (Zhu and Alva 1993). Cu leaching through the soil profile and the possible toxic effects on trees can be mitigated by raising soil pH and/or building up organic matter content in the soil (Alva et al. 1995) or by applying gypsum to reduce soil toxicity (Alva et al. 1993).

The aims of this review are to (i) highlight both benefits and risks related to the use of CBACs, (ii) identify potential for their improvement and opportunities for further research, and (iii) list alternatives to CBACs which are either developed, but not yet in use or already available on the market.

2 Copper biocides used for crop protection

Copper is an essential micronutrient for all living organisms including plants and it acts as a cofactor for several enzymes involved in respiration and electron transport proteins (Sommer 1931). At the same time, Cu acts as a broad-spectrum biocide at higher concentrations due to its interaction with nucleic acids, disruption of enzyme active sites, interference with the energy transport system, and finally the disruption of the integrity of cell membranes (Fleming and Trevors 1989). A number of inorganic Cu formulations have been developed and used as biocides to contain plant pathogenic bacteria, fungi, oomycetes and in some instances, invertebrates and algae (Schüder et al. 2004; Capinera and Dickens 2016) (Table 1). In addition to the direct application on plants in the field, CBACs are also used for seed treatment to prevent infection of seedlings by plant pathogens (Carisse et al. 2000; Verma et al. 2011).

Table 1 Most commonly used antimicrobial copper compounds for foliar disease management caused by plant pathogenic bacteria, fungi, and oomycetes

Name of active ingredient[a]	Chemical formula	CAS number
Basic copper sulfate	$CuSO_4 3Cu(OH)_2$	1344-73-6
Basic copper carbonate	$CuCO3Cu(OH)_2$	12069-69-1
Copper chloride	$CuCl_2$	7447-39-4
Copper hydroxide	$Cu(OH)_2$	20427-59-2
Copper oxide	Cu_2O	1317-38-0
Copper oxychloride	$3Cu(OH)_2CuCl_2$	1332-40-7
Copper oxychloride sulfate	$(Cu_4(OH)6(SO_4))$	8012-69-9
Copper sulfate pentahydrate[2]	$CuSO_4 5H_2O$	7758-99-8

[a] Active ingredients contained in copper-based antimicrobials and their commercial name may widely vary from one country to another

A wide availability of CBACs has facilitated foliar disease management of a number of annual and perennial crops. CBACs are mainly used to manage diseases, especially in organic agriculture since the application of conventional fungicides is forbidden in this system. Among the most important crop diseases in organic farming managed with CBACs, there are diseases caused by oomycetes such as downy mildew of grapevine (Dagostin et al. 2011; Tamm et al. 2015) and late blight of potato (Ghorbani et al. 2004; Finckh et al. 2006; Speiser et al. 2006; Finckh et al. 2015). However, other foliar diseases which are difficult to manage without fungicides also benefit from the use of CBACs including apple scab (Holb and Heijne 2001; Holb et al. 2003), and various coffee diseases (Hindorf et al. 2015; Souza et al. 2015). CBACs are important, even in conventional agriculture due to their low costs and are an alternative product when registered fungicides are banned due to their negative effects on human health and biodiversity. This is especially the case for minor crops in which a number of previously registered pesticides are no longer available (Lamichhane et al. 2015).

Unlike a wide range of fungicides available to manage crop diseases caused by plant pathogenic fungi, there are only a few bactericides available to protect crops. Consequently, often CBACs are the only means available for growers both in conventional and organic farming to manage diseases caused by plant pathogenic bacteria both of annual and perennial crops including tomato spot (Jones et al. 1991; Roberts et al. 2008), citrus canker (Behlau et al. 2010; Behlau et al. 2017), fire blight of pome fruits (Elkins et al. 2015), walnut blight (Lee et al. 1993; Ninot et al. 2002), stone fruit canker (Olson and Jones 1985; Wimalajeewa et al. 1991; Sayler and Kirkpatrick 2003), mango apical necrosis (Cazorla et al. 2006), and olive knot (Teviotdale and Krueger 2004). Exceptions are fire blight of pome fruits and bacterial canker of kiwifruit, for which a large number of biological control agents are available (Vanneste 2011; Vanneste 2013).

3 Risks due to the excessive use of inorganic copper in agriculture

The intensive use of the CBACs for more than one century has led to a number of impacts related to human health and the biodiversity. Overall, there are both direct and indirect negative effects of these compounds when they are applied to crops to manage crop diseases which are described below.

3.1 Phytotoxicity

High levels of Cu in agricultural soil may cause plant stress and reduce soil fertility having adverse effects on crop yield and quality (Dumestre et al. 1993). Copper compounds release Cu ions when they are dissolved in water and thus an excessive uptake of Cu ions by plants at any time may lead to damage, also known as phytotoxicity (Fig. 2). Many factors might lead to Cu phytotoxicity on plants, including the application of highly soluble Cu formulations (e.g., copper sulfate, copper nitrate) or excessive amounts (either too high application rate or too frequent applications), use of acidic spray solution (pH below 5.5) which results in excess soluble Cu, tank mixing of Cu with other products, application of Cu at high temperatures, dry weather and presence of impurities in the product (Timmer and Zitko 1996; Behlau et al. 2017). In addition, wet plant canopies, due to a high humidity of the environment, favor a continuous release of Cu ions with consequent phytotoxic effects. Finally, the application of CBACs at certain plant stages may cause phytotoxic effects as many plants are sensitive to Cu compounds even at lower concentration (e.g., during flushing or blooming; Renick et al. 2008). Overall, many perennial fruit tree crops express frequent symptoms of Cu phytotoxicity, especially when they are at the blooming phase, compared to annual crops. For instance, phytotoxic effects of Cu have been observed on tomato, apple (Lesnik et al. 2011), pear (Reil et al. 1974), cherry (Holb and Schnabel 2005), and citrus (Schutte et al. 1997). Because the amount and dynamics of copper content in the soil and leaves differ from organic to integrated production system (Holb and Nagy 2009), phytotoxic effects on a given crop may differ between these systems.

Fig. 2 Characteristic symptoms of phytotoxicity due to copper-based antimicrobial compounds on citrus fruit surface. Such a visible damage on fruit surface markedly reduces the esthetic value of the fruits thereby compromising their marketability

In addition to the aboveground parts, Cu in high concentration is toxic to plant roots as it interferes with the uptake of iron and other nutrients, especially in acidic soils where pH is not well-controlled. This is particularly the case for Cu-sensitive crops grown in rotation with copper-treated crops. High levels of Cu application to soil and leaves seriously impaired normal growth of tomato plants, which showed significant reduction in yield, fruit number, dry root biomass, and plant height, with increasing levels of Cu application to soil (Sonmez et al. 2006). Cu has been also reported to reduce seed germination and seedling emergence. For instance, Cu is toxic to sunflower seedlings which is due to the induction of oxidative stress (Pena et al. 2011). The germination rate of several crops, including sunflower (Pena et al. 2011), bean (Sfaxi-Bousbih et al. 2010), wheat (Singh et al. 2007), and maize (Mocquot et al. 1996; Boros and Micle 2015), is reduced by Cu stress. Finally, seed germination and seedling emergence of barley could be directly affected by the type of water used for irrigation when Cu was present in high concentration in soil (Stephenson et al. 2001).

Typical symptoms of Cu phytotoxicity on leaves consist of chlorosis, darkening of axial and abaxial surfaces, necrotic spots, and leaf margin burn. On fruit, Cu may cause value-depreciating blemishes such as corky, dark, and star-shaped lesions. Overall, plants may show loss of vigor and/or stunted growth (Lepp 1981; Woolhouse and Walker 1981; Jones 1991; Timmer and Zitko 1996; Dagostin et al. 2011).

3.2 Development of copper-resistant strains

While CBACs have multisite activity with a low risk of pathogens developing resistance, several cases of resistance developed by plant pathogenic bacteria are reported worldwide (Table 2). The number of such reports has markedly increased since the 1980s (Marco and Stall 1983; Martin et al. 2004). When a given bacterial strain has developed resistance to Cu, it continues to multiply without being affected by copper treatments at standard concentrations. This problem is particularly acute in certain crop diseases such as bacterial spot of tomato, caused by xanthomonads, which mainly relies on CBACs. In Florida, *Xanthomonas perforans* strains isolated from bacterial spot of tomato lesions in the tomato production areas in 2006 were found to be resistant to Cu (Horvath et al. 2012). As a consequence, management of bacterial diseases of crops has been exceedingly difficult and has resulted in reduced disease control.

Table 2 A non-exhaustive list of reports available in the literature on copper resistance developed by plant pathogens since 2001

Continent	Country	Targeted disease	Host	Causal agent	References
Asia-Pacific	Australia	Bacterial spot	Pepper	*Xanthomonas vesicatoria*	Martin et al. (2004)
	Japan	Bacterial canker	Kiwifruit	*Pseudomonas syringae*	Masami et al. (2004)
	New Zealand	Bacterial canker	Stone fruit	*Xanthomonas arboricola*	Vanneste et al. (2005)
	New Zealand	Bacterial spot	–	*Xanthomonas vesicatoria*	Behlau et al. (2013)
	New Zealand	Bacterial canker	Apple	*Pseudomonas syringae*	Vanneste et al. (2008)
	New Zealand	Bacterial canker	Kiwifruit	*Pseudomonas syringae*	Colombi et al. (2017)
	Syria	Fire blight	Apple	*Erwinia amylovora*	Al-Daoude et al. (2009)
	Turkey	Bacterial spot	Pepper	*Xanthomonas* spp.	Mirik et al. (2007)
Africa	Tanzania	Bacterial spot	Tomato	*Pseudomonas syringae*	Shenge et al. (2008)
Europe	France	Citrus canker	Citrus	*Xanthomonas citri* subsp. *citri*	Richard et al. (2017)
			Pepper	*Xanthomonas gardnerii*	Richard et al. (2017)
	Germany	Plum decline	Plum	*Pseudomonas syringae*	Hinrichs-Berger (2004)
	Italy	Bacterial canker	Kiwifruit	*Pseudomonas syringae*	Marcelletti et al. (2011)
	Italy	Apical necrosis	Mango	*Pseudomonas syringae*	Aiello et al. (2015)
	Italy	Bacterial blight	Walnut	*Xanthomonas arboricola*	Behlau et al. (2013)
	Portugal	Bacterial blight	Walnut	*Xanthomonas arboricola*	Scortichini et al. (2001)
	Spain	Bacterial spot	–	*Xanthomonas euvesicatoria*	Behlau et al. (2013)
North America	Canada	Bacterial speck	Tomato	*Xanthomonas* spp.	Abbasi et al. (2015)
	Canada	Fire blight	Apple	*Erwinia amylovora*	Sholberg et al. (2001)
	USA	Bacterial canker	Sweet cherry	*Pseudomonas syringae*	Renick et al. (2008)
	USA	Bacterial spot	Citrus	*Xanthomonas alfalfae* subsp. *citrumelonis*	Behlau et al. (2011)
	USA	Bacterial spot	–	*Xanthomonas vesicatoria; X. euvesicatoria*	Behlau et al. (2013)
	USA	Citrus canker	Citrus	*Xanthomonas axonopodis*	Behlau et al. (2012)
	USA	Halo blight	Snap bean	*Pseudomonas syringae*	Zhang et al. (2017)
	USA	Bacterial spot	Tomato	*Xanthomonas perforans*	Behlau et al. (2013)
South America	Argentina	Pith necrosis	Tomato and pepper	*Pseudomonas* spp.	Alippi et al. (2003)
	Argentina	Citrus canker	Citrus	*Xanthomonas citri* subsp. *citri*	Behlau et al. (2011)
	Brazil	Bacterial spot	Tomato	*Xanthomonas* spp.	Quezado-Duval et al. (2003); Araújo et al. (2012)
	Brazil	Bacterial canker	Grapevine	*Xanthomonas campestris*	Marques et al. (2009)
Central America and Caribbean	Mexico	Bacterial spot	–	*Xanthomonas euvesicatoria*	Behlau et al. (2013)
	Guadaloupe	Bacterial spot	–	*Xanthomonas euvesicatoria*	Behlau et al. (2013)
	Puerto Rico	Bacterial spot	–	*Xanthomonas euvesicatoria*	Behlau et al. (2013)
	US Virgin Islands	Bacterial spot	–	*Xanthomonas euvesicatoria*	Behlau et al. (2013)
	Costa Rica	Bacterial spot	–	*Xanthomonas euvesicatoria*	Behlau et al. (2013)
	Barbados	Bacterial spot	–	*Xanthomonas euvesicatoria*	Behlau et al. (2013)
	Trinidad	Black rot	Crucifers	*Xanthomonas campestris*	Lugo et al. (2013)

Despite the development of Cu-resistant bacterial strains, CBACs are routinely used as a standard treatment to manage foliar diseases (Fig. 3). In epidemic years, repeated application of this compound over several seasons and years may be necessary to minimize crop loss. This has markedly increased the risk of insufficient disease management which has been reported by several studies (Marco and Stall 1983; Canteros 1999; Stirling et al. 1999; Cazorla et al. 2006). Indeed, when a bacterial strain has acquired Cu resistance, the continuous selection pressure gradually increases the frequency of the resistant pathogen population and compromises the efficacy of Cu (Sundin et al. 1989). This is especially true on perennial crops where epiphytic and partially endophytic nature of most plant pathogenic bacteria (Renick et al. 2008) might provide a reservoir of Cu resistance genes that could be acquired by Cu-sensitive strains (Cazorla et al. 2002; Behlau et al. 2012). Because many bacterial populations thrive on the same host, there is risk for horizontal gene transfer of Cu resistance determinants (Cooksey 1990; Voloudakis et al. 1993; Behlau et al. 2012). It is highly improbable that bacteria become resistant to Cu through spontaneous mutations since Cu resistance is regulated by several genes in bacteria (Cooksey 1990). Chromosomal transfer of the Cu resistance plasmids may occur in nature (Bender et al. 1990; Basim et al. 1999), or in experimental conditions (Stall et al. 1986; Voloudakis et al. 1993) which points out the probability that copper resistance plasmids can be shared among different genotypes of bacterial pathogens as already demonstrated (Bender and Cooksey 1986; Cooksey 1990; Behlau et al. 2012). However, it seems that the plasmid transfer frequency is the highest between

Fig. 3 Application of copper-based antimicrobial compounds on citrus trees in Brazil. While there are reports on the development of Cu resistant strains of *Xanthomonas citri* subsp. *citri*, the causal agent of citrus canker, from Argentina and France (Table 2), there are no such records in Brazil. Consequently, judicious use of these compounds have become an important component of integrated pest management to reduce the pathogen population development

strains when Cu-resistant strains thrive in the same environment (Sundin et al. 1989).

To date, plant pathogenic bacterial species within many genera have acquired resistance to CBACs including pseudomonads, xanthomonads, and *Erwinia* (Table 2). Most of the copper-resistant genes in plant pathogenic bacteria are located on plasmids (Bender and Cooksey 1986; Bender et al. 1990; Cazorla et al. 2002; Behlau et al. 2012). There are only a few reports of Cu resistance genes located on the chromosome (Lee et al. 1994; Basim et al. 2005). Indeed, copper sequestration and copper efflux have been suggested as the key mechanisms for copper resistance in bacteria (Cooksey 1993). Because some heavy metals, including Cu, are able to activate the production of siderophores by bacteria, siderophores could affect heavy metal tolerance (Schalk et al. 2011). This results from siderophores chelating heavy metals (Braud et al. 2009) and sequestering them in the extracellular medium outside of the bacterium preventing their diffusion across the bacterial membranes into the cytosol of the cell (Braud et al. 2010), thereby permitting bacteria to be more resistant to Cu. Copper sequestration may also occur in the periplasm of bacterial cells. In that case, copper resistance genes encode for copper-binding proteins that prevent copper ions from harming the cell (Cha and Cooksey 1991; Cha and Cooksey 1993).

The development of resistance by most important groups of plant pathogenic bacteria to CBACs raises a serious concern, thereby challenging the sustainability of current crop protection systems. Few effective substitutes to these compounds are available to date, which leaves no alternatives for growers to protect their crops. The continuous application of these compounds in an environment already harboring resistant strains of the pathogen is threatening the viability of the entire cropping system and thus compels marketing of existing alternative biological control products registered in several countries and to find more sustainable solutions to CBACs, including the re-design of the entire cropping system.

3.3 Soil accumulation and negative effects on soil biota

Crop protection based on a long history of CBACs has resulted in accumulations of Cu in surface horizons thereby affecting a large portion of agricultural land. However, despite a general knowledge that CBACs are widely used worldwide, there is a serious lack of data on the amount of Cu used in agriculture. Few quantitative data reported in the literature are likely to suggest a massive use of these compounds such as that reported from Australia where over 7500 t per year only of CBACs were used during the 1990s (Lepp et al. 1994). In viticulture, Cu is applied at rates of up to 80 kg/ha per annum (Rusjan et al. 2007). Because multiple applications of CBACs are made within a single growing season, the total amount of these compounds used in agriculture per annum might be very high. For example, on the north coast of New South Wales in Australia, Cu was applied up to 15 times per year against anthracnose (*Colletotrichum gloeosporoides*) in avocado orchards (Van Zwieten et al. 2004). In Brazil, almost 30 kg metallic copper/ha/year is used to be sprayed on orchards for control of citrus canker. Currently, successful disease control has been achieved in Brazil (Behlau et al. 2017) and Florida (Graham et al. 2011) with less than a third of that annual rate.

The prolonged application of CBACs for over a century has resulted in accumulation of this heavy metal in the soil in general and in the topsoil in particular as Cu extract residues typically accumulate in the upper 15 cm of soil. Indeed, a number of studies have reported the accumulation of Cu in agricultural soil worldwide (Table 3). However, it is difficult to assess whether or not such a high level of Cu is only due to the application of CBACs since copper occurs naturally in soils. Soil Cu is posing a higher risk in perennial crops, in particular vineyards as some of them contain 40–50 times more Cu than uncontaminated soils (Table 3). However, the potential toxicity of Cu varies from one soil to another independently of the concentration of Cu accumulated in the soil. For example, alkaline soils with increased calcium availability ameliorate the effects of Cu phytotoxicity (Alva et al. 1993). Downward movement of copper through the soil profile is greater in sandy soils than soils rich in clay or organic matter (Alva et al. 1995). Furthermore, copper availability and toxicity in the soil is greatly increased as the soil pH decreases below 5.5 (Fan et al. 2011).

Copper is potentially toxic to the soil biota including an extremely diverse array of micro- (bacteria and fungi) and macroorganisms (protozoa, nematodes, mites, springtails, spiders, insects, and earthworms). These soil biota play an important role in the "soil food web," ranging from residue decomposition to nutrient storage and release, soil structure and stability, resistance against pathogens, and degradation or immobilization of pesticides and other pollutants (Kent and Triplett 2002). Therefore, soil biota, which

Table 3 Reports of high soil copper residues across major cropping systems worldwide. Uncontaminated soils generally have < 20 mg Cu/kg soil, but when copper is present in parent rock and natural minerals, as much as 100 mg Cu/kg is possible (McBride et al. 1981; Wightwick et al. 2008)

Continent	Country	Type of crop	Total copper concentration (mg/kg of soil)[a]	References
Asia-Pacific	Australia	Vineyard	60–340	Merrington et al. (2002)
	New Zealand	Vineyard	1–259	Morgan and Taylor (2004); Robinson et al. (2006)
	New Zealand	Stone fruit orchards	21–490	Gaw et al. (2003)
	Taiwan	Vineyard	9.1–100	Lai et al. (2010)
Africa	South Africa	Vineyard	10–20	Eijsackers et al. (2005)
	Tanzania	Coffee orchard	24–366	Senkondo et al. (2014)
Europe	France	Vineyard	57–1500	Brun et al. (1998); Besnard et al. (2001); Parat et al. (2002)
	Italy	Vineyard	93–478	Dell'Amico et al. (2008); Provenzano et al. (2010)
	Portugal	Vineyard	8–574	Pessanha et al. (2010)
	Serbia	Vineyard	24–432	Ristic et al. (2006)
	Slovenia	Vineyard	65–120	Rusjan et al. (2006), (2007)
	Spain	Vineyard	41.5–583.1	Fernández-Calviño et al. (2008); Fernández-Calviño et al. (2009)
North America	USA	Vineyard	87–142	Taschenberg et al. (1961)
	USA	Citrus orchard	Up to 250	Yang et al. (2009)
South America	Brazil	Vineyard	36–3215	Mirlean et al. (2007); Nachtigall et al. (2007)

[a] The concentration of copper in the soil of a given orchard/vineyard depends also from the soil type and it increases over the year due to its accumulation with repeated application. Only minimum and maximum copper concentration identified in these studies are indicated in the table

represent an important component of soil health, are affected by Cu residues in the soil. This is especially the case of microorganisms as they are generally more sensitive to heavy metals than other organisms (Giller et al. 1998). For example, adverse effects of heavy metals on microbial activity and functions (Kandeler et al. 1996; Merrington et al. 2002) finally may impact bioturbation, which consists in the churning and stirring of sediment by organisms (Bates and Jackson 1984). A previous study (Kandeler et al. 1996) showed that microbial biomass, enzyme activity, and functional diversity of soil microbial communities decreased with increasing Cu pollution at 100 mg/kg Cu in different types of soil. In addition, both microbial biomass and metabolic quotient were reduced when there was an increase in Cu concentration in the soil (Khan and Scullion 2000). A shift in microbial community structure due to an increased concentration of Cu was previously reported (Wang et al. 2007; Deng et al. 2009). Potential negative effects also have been observed on many macroorganisms including earthworm populations (Van Zwieten et al. 2004; Eijsackers et al. 2005), nematodes (Jaworska and Gorczyca 2002), and snails (Rogevich et al. 2008). In most soils, Cu residues are likely to remain indefinitely and will continue to influence the health of the soil (Van Zwieten et al. 2004).

Elevated levels of Cu may cause the contamination of surface and subsurface waters (Fernández-Calviño et al. 2008; Fernández-Calviño et al. 2009). On the other hand, it is not easy to deduce whether applied forms of (inorganic) Cu could be identified in groundwater or they have any significant impact on water quality and aquatic environments although Cu might enter water resources when they are not properly applied or through accidental spill (Unwin et al. 1995).

3.4 Possible impact on food quality parameters

Elevated levels of Cu may pose public health problems if soil Cu enters the food chain. The European Union regulations enforce maximum Cu residue levels (i.e., 5 mg/kg fresh mass in or on foods). However, agricultural goods with levels of Cu residues exceeding this legal threshold are reported (Kurnik et al. 2012). These copper spray residues may have adverse effects on agricultural products, on both external and internal quality parameters including appearance or taste. An example is russeting, which may also impact marketing of the affected fruit crops (Reil et al. 1974; Teviotdale et al. 1997). However, growers learned to manage this problem by very careful timing of Cu applications.

4 Regulation and or restriction to limit the use of inorganic copper in agriculture

Like all compounds with toxic effects, CBACs are also regulated products with certain limit posed in the total dosage applied to prevent the potential risks due to buildup of toxic levels in the environment. For example, in many parts of the world, copper sulfates are no longer recommended for use given that sulfates are highly soluble and toxic to the spray applicators and the environment (Mackie et al. 2012). As a consequence, the use of less-soluble Cu formulations, such as Cu hydroxide and Cu oxychloride, are encouraged.

The European Union introduced legislation limiting the use of Cu compounds by regulation no. 473/2002 (Anonymous 2002). The limit posed in the total quantity of Cu began since 2000 in Europe with the basic standard of the International Federation of Organic Agriculture Movements which imposed a limit of 8 kg/ha (Van Zwieten et al. 2004). Subsequently, the EU regulation (Reg. 473/2002) took that limit and adjusted it so as to reduce the use of Cu gradually over the years. As a result, the limit was 8 kg/ha/year until 2005, which further reduced to 6 kg/ha/year (with the possibility to make an average over 5 years in perennial crops).

Besides the EU, the use of CBACs in organic farming is restricted in many other countries. For example, in Australia, the use of Cu sulfate and hydrated lime mixtures, Cu hydroxide, and Cu sulfates are allowed by certifying authorities but the use of Cu oxychloride is prohibited (Van Zwieten et al. 2004). In addition, since 2002, the total Cu input in organic farming in Australia should not exceed 8 kg/ha/year, as regulated by the International Federation of Organic Agriculture Movements.

In the USA, CBACs are on the National Organic Program List as synthetics (https://www.ams.usda.gov/rules-regulations/organic/national-list) and they are regulated for use as disease management tools, with the restriction that they must be used in a manner that minimizes Cu accumulation in the soil. However, labels for CBACs do not indicate the potential negative effects of these compounds on soil and water biota, nor do they indicate the potential of Cu compounds in reducing the sustainable soil productivity due to their prolonged use in fields (Epstein and Bassein 2001). Indeed, the only environmental caution on US Cu pesticide labels concerns toxicity to fish and aquatic organisms, and phytotoxicity to Cu-sensitive cultivars.

Therefore, the use of Cu is quite controversial, especially in organic farming and some authors already predict that its use may be banned in the near future (Wightwick et al. 2008; Finckh et al. 2015; Tamm et al. 2015). While the application of Cu is likely limited to 6 kg/ha/year in most European countries, including Italy, France, and Spain, a lower quantitative limit of 3 to 4 kg/ha/year has been imposed in Germany, Austria, and Switzerland (Wightwick et al. 2008; Finckh et al. 2015; Tamm et al. 2015). CBACs are banned for organic and conventional farming in other EU countries such as the Netherlands and Denmark. Taking into account the recent evolution in legislation related to the use of Cu in organic farming, additional restrictions are expected in the near future in the maximum quantity of CBACs utilizable. This is especially true while considering that the approval period for Cu products in part A of the annex to Reg. 540/2011 is expired by the end of January 2018. Finally, restriction of CBACs may also result in the increased use of Cu-leaf fertilizers with an intended use against plant pathogens.

5 Mitigation strategies to contain negative effects of copper-based microbial compounds

5.1 Optimized use of copper

Overall, the average number of Cu sprays needed per season may differ from organic to integrated production systems with up to 15 sprays per season in organic viticulture. The number of sprays mainly depends on the availability of susceptible plant tissues, presence of Cu-sensitive plant tissues (e.g., apple fruit stages sensitive to russeting), environmental conditions, and adoption of certain agronomic practices (Stall and Seymour 1983; Leite and Mohan 1990). However, adoption of best management practices may significantly reduce the number of sprays since more frequent sprays and at higher doses may not necessarily result in significant increases in disease control (Behlau et al. 2017). Because Cu is often applied in very high concentration and not always in a timely manner in many parts of the world (Fig. 4), reduction in the rate and number of applications per season still is the focus of Cu reduction strategies developed in many countries. In addition, drifts need to be avoided through the adoption of optimized application techniques.

During the last two decades, more effective use of Cu has been achieved based mainly on monitoring and forecasting systems (Van Zwieten et al. 2004). In particular, choice of optimal application timing, advanced spraying technology, and advanced formulations of Cu fungicides have led to more efficient use of CBACs. In addition, evidence that effective disease management can be achieved also with low amounts of Cu has encouraged growers toward a sparing use of these compounds, which is profitable for growers in terms of costs related to the product and application. Reduction of Cu concentration would lower the risk of phytotoxicity, which is

Fig. 4 Tomato fruit surfaces showing residues of copper-based antimicrobial compounds (light green spots) used to contain the build-up of bacterial populations on plant or fruit surfaces. The lack of timely application of these compounds, however, did not control bacterial spot, caused by *Xanthomonas perforans*, with heavy disease symptoms on tomato fruits (black spots). Tomato fruits bearing such disease symptoms are not marketable given their reduced esthetic values

another reason for growers to reduce the quantity of CBACs used in their field.

Besides spray concentration, spray volume rate also affects the total amount of Cu applied. An in-depth investigation on the effect of CBACs droplet density and size on the development and multiplication of the target pathogen could potentially allow to reduce the spray volumes generally applied to manage a given disease. Adjustment of the spray volume rate to the size and density of the canopy is another parameter to be considered for optimized application efficiency of CBACs. Several studies have demonstrated that the total quantity of Cu compounds can be markedly reduced by adjusting the rate of spray volume to the effective plant canopy size, which is especially the case on perennial crops (Walklate et al. 2006; Solanelles et al. 2006; da Silva Scapin et al. 2015). In perennial crops, it is common to use predetermined copper rates and spray volumes, which are indiscriminately applied to orchards of different ages and sizes leading to a waste of resources, such as water, energy, and chemicals and to environmental pollution. However, use of copper on these crops should be based on the volume of the tree canopy or the tree-row-volume to be treated per hectare (Sutton and Unrath 1984; Sutton and Unrath 1988; Rüegg and Viret 1999; Pergher and Petris 2008; Sanchez-Hermosilla et al. 2013; da Silva Scapin et al. 2015). For instance, in Brazil, use of tree-row-volume-based copper rates for control of citrus canker has allowed for the copper rates to be downsized to less than one third of former rates without affecting quality of disease control (da Silva Scapin et al. 2015; Behlau et al. 2017).

Appropriate timing of application is a critical factor both to reduce the frequency of spray and to increase the effectiveness of the application. Because Cu is a contact material and does not penetrate to internal plant tissues (inside dormant buds, knots, or cankers) to affect pathogen populations, its applications have to be timed to coincide with periods when the host is susceptible, when the pathogen is accessible, and when conditions are favorable to disease (Kennelly et al. 2007). For example, plant tissues are more susceptible to bacterial pathogen during the early growth stage than the advanced one (ontogenic resistance) so Cu spray could be avoided in that case. Likewise, if growers want to apply Cu on fruit trees during bloom, they have to reduce its concentration (to avoid phytotoxicity), but such reduced level of Cu is highly ineffective in lowering pathogen populations on blossoms, and thus, such interventions must be avoided.

The use of reduced doses in combination with effective cultural practices is another way to optimize the use of CBACs. The choice of correct formulation and enhancement of solubility also optimizes use of Cu. For example, exudates released from the plant and microorganisms form weak acids that lower the pH of water on plant surface, thereby increasing Cu solubility and availability (Arman and Wain 1958).

Tank mixing could be an important way to increase the effectiveness of treatment and reduce to some extent the quantity of CBACs. For example, the use of Cu with iron has been reported to enhance the effectiveness of Cu against plant pathogenic bacteria (Lee et al. 1993), although the potential negative effects of adding iron should be well assessed, given that iron is also a heavy metal. Combining Cu with ethylene bisdithiocarbamate fungicides, such as maneb or mancozeb, also enhances the availability of free Cu ions (Marco and Stall 1983). Use of small molecules, such as 2-aminoimidazole as additives in the tank mixes (Worthington et al. 2012) and tank mixing with famoxadone and cymoxanil (Roberts et al. 2008; Fayette et al. 2012) also have been reported to be effective for bacterial disease management especially to combat Cu-resistant strains.

5.2 Soil remediation

A Cu concentration of over 30 mg/kg in soils can cause toxicity to plants although several factors affect it including plant species, growth stage and plant organ, cultivation practices and environmental conditions (Lepp 1981; Woolhouse and Walker 1981). There are several remediation strategies to counterbalance the excess levels of Cu in soil including Cu immobilization by altering soil pH through application of lime in soils or by adding iron (Fe) because of its antagonist relationship with Cu as well as building up organic matter content in the soil (Alva et al. 1995; Römkens et al. 2004; Schilling and Cooper 2004). However, all these remediation strategies are only a temporary solution since continuous use of Cu leads to significant accumulation over time. Furthermore, acidifying air pollutants may counteract attempts to avoid Cu toxicity via decreasing pH levels. Other remediation strategies such as Cu removal, sequestration, and phytoextraction have been recently reviewed (Mackie et al. 2012), although none of them are likely to provide a long-term practical solution.

5.3 Alternatives to copper compounds

Replacing CBACs with other less harmful products for plant disease control is a major challenge. This is mainly due to the many positive aforementioned attributes of CBACs, especially their broad spectrum activity, as well as the paucity of robust and scientifically proven alternatives. Nonetheless, the growing demand to restrict the annual amount of Cu sprayed in agriculture has encouraged research efforts to reduce the CBACs dependence in agriculture. To date, a number of non-Cu-based products and biological control agents showed some effectiveness against many plant diseases (Table 4). In particular, biological control agents including resistance inducers and nanoparticle-based metallic formulations are the most promising alternatives to CBACs in a short term.

In biological control, formulations of selected antagonistic strains of bacteria or fungi are applied. More than 209 microbial strains have been registered in different regions for commercial use in biological control of which 94 have registration for disease control (van Lenteren et al. 2018). Characteristically, biological control agents (BCAs) have a narrow spectrum of activity with low risk of negative impact on biodiversity. Their activity is often based on a combination of different modes of action (including induction of resistance of the host plant) with low risks of resistance development in the targeted pathogen populations. For the control of diseases commonly done by CBACs, some BCA solutions are already commercially available (van Lenteren et al. 2018). Products based on *Aureobasidium pullulans* DSM 14940 and 14941 (registered in EU, Canada, and the USA), *Pantoea agglomerans* C9-1 (registered in Canada and the USA), *Pantoea agglomerans* E325 (registered in Canada), *Pantoea agglomerans* p10c (registered in New Zealand), and *Pseudomonas fluorescens* A506 (registered in the USA) are available for fire blight control in pome fruits. *Pseudomonas rhodesiae* HAI-0804 is available in Japan for *Pseudomonas syringae* control in plum. *Bacillus pumilis* QST 2808 and *Bacillus subtilis* QST713 are registered in the USA for control of *Venturia* spp. (https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/decision_PC-006485_16-Nov-04.pdf; https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/decision_PC-006479_9-Aug-06.pdf). Bacteriophages have been registered for control of *Clavibacter michinganensis* spp. *michiganensis* and *Xanthomonas campestris* pv. *vesicatoria* in the USA. *Pseudomonas fluorescens* CL145A has registration for control of bacterial rots in lettuce and cabbage in Japan.

The systemic acquired resistance inducers are one of the options to confer protection against plant pathogens (Vallad and Goodman 2004; Francis et al. 2009; Graham et al. 2013, 2016). In addition, hexanoic acid (Aranega-Bou et al. 2014; Llorens et al. 2015), polysaccharides (Trouvelot et al. 2008; Ma et al. 2013; Abouraïcha et al. 2015), and vitamins (Dong and Beer 2000; Boubakri et al. 2013) are also reported to induce some degree of plant resistance. However, the mode of action and the potential of these compounds in crop protection have not been fully studied yet which has limited their use in agriculture.

Application of nanoparticles in agriculture is another novel approach that has been proving very effective against plant pathogens (Jayaseelan et al. 2012; Khot et al. 2012; Krishnaraj et al. 2012). Greenhouse and field trials have shown that nanoparticle-based silver and zinc formulations are equally to or more efficient than CBACs in reducing bacterial and fungal diseases on tomato and citrus (Ocsoy et al. 2013; Graham et al. 2016; Strayer et al. 2016; Young et al. 2017; Strayer et al. 2018). This is because most CBACs used in agriculture contain micron-sized insoluble metallic copper compounds, such

Table 4 An incomplete list of products/substances which can be considered as alternatives to copper compounds

Product[a]	Targeted plant pathogens	Reference
Potassium bicarbonate	Fungi	Ilhan et al. (2006); Jamar et al. (2007)
Potassium carbonates	Fungi	Holb and Kunz (2016)
Potassium phosphonates	Oomycetes	Speiser et al. (2000)
Silicon gel	Bacteria	Gutiérrez-Barranquero et al. (2012)
Chitosan	Bacteria, fungi and oomycetes	Scortichini (2014); Romanazzi et al. (2016)
Lime sulfur	Fungi	Holb and Heijne (2001); Holb et al. (2003)
Acibenzolar-S-methyl	Bacteria and fungi	Baysal and Zeller (2004); Gu et al. (2013)
Plant extracts	Bacteria, oomycetes	Baysal and Zeller (2004); Dagostin et al. (2011)
DNA-directed silver (Ag) nanoparticles	Bacteria	Ocsoy et al. (2013)
Nano-formulated zinc oxide	Bacteria	Graham et al. (2016)
Clay	Oomycetes	Dagostin et al. (2011)
Systemic resistance inducers	Bacteria	Graham and Myers (2013), (2016)
Bacteriophages	Bacteria	Flaherty et al. (2000); Jones et al. (2007); Lang et al. (2007)
Small molecule additive	Bacteria	Worthington et al. (2012)
Laminarin	Oomycetes	Aziz et al. (2003); Copping and Duke (2007)
Aureobasidium pullulans	Fungi	Holb and Kunz (2013)
Cladosporium cladosporioides	Fungi (apple scab)	Köhl et al. (2015)
Trichoderma spp.	Oomycetes	Hanada et al. (2008); Rossi and Pattori (2009); Jacometti et al. (2010)

[a] Some of these products have no antimicrobial activity per se but they stimulate the plant's natural defense mechanism and render them much less susceptible to pathogen's attack and they act as a systemic acquired resistance (SAR) inducer

as copper hydroxide, copper oxide, or copper oxychloride (Richardson 1997). Moreover, because fixed copper particles are hydrophobic, they aggregate in water and reduce the surface area of metallic particles thereby decreasing their antibacterial activity (Bae et al. 2010). Conversely, nanoparticles have unique physical and chemical properties at the cellular, atomic, and molecular levels (Emerich and Thanos 2006). The smaller size and higher surface-to-volume ratio of the nano-sized compounds allow metallic particles to penetrate microbial membranes and release metal ions into solution more efficiently than the micron-sized compounds (Panacek et al. 2006) conferring the nanometer-sized metallic compounds a higher antibacterial activity compared with the micron-sized formulations (Yamamoto 2001; Jiang et al. 2009). Before any nanopesticides will become available in agriculture, possible specific risks for human health and environment, e.g., for soil biota, must be assessed. A legal framework for such a risk assessment is still missing in the EU and may, together with possible public perceptions, not favor the use of nanopesticides.

Research has explored the potential of many other substances as alternatives to CBACs which is also due to evolving legislations (Table 4). For instance, replacement and/or reduction of CBACs is a declared priority in the EU organic legislation as described in the Regulation 473/2002 (Anonymous 2002). Consequently, focusing on alternative products to CBACs represents a priority in many European countries. As a result, several projects based on biological control and use of plant extracts were funded to screen and develop alternatives to CBACs such as Blight-MOP (2001–2005), REPCO (2003–2007), CO-FREE (2012–2016), and ProLarix (2013–2015) which have served as the starting point for the development of such alternatives. In particular, main findings and conclusions of Blight-MOP, which focused on potato late blight, were that planting resistant varieties would be the most effective strategy against blight which later has been confirmed by CO-FREE. Copper-free alternative agents such as extracts of manure-based composts, micro-organisms and plant extracts had either no or limited effects on blight compared with standard CBACs. In REPCO more than 110 plant extracts or other compounds suitable for use in organic farming have been assessed for their potential to control downy mildew in screening experiments in grapevine and more than 100 plant extracts or other compounds have been tested against scab. A satisfactory level of downy mildew control in grapevine has been obtained by using *Yucca schidigera* and *Salvia officinalis* extracts as well as *Trichoderma harzianum* (Dagostin et al. 2011). Likewise, *Yucca schidigera* extracts allowed a good level of scab control in apple (Bengtsson et al. 2009). Application of vinasse on leaf residues stimulated leaf degradation and reduction of *Venturia inaequalis* ascospore production, offering a good management option in apple orchards (Heijne et al. 2007). Among 200 candidate antagonists, the novel antagonist *Cladosporium cladosporioides* H39 showed a high efficacy against *Venturia inaequalis* (Köhl et al. 2009). In the first field trials, this antagonist reduced apple scab incidence on fruits by 41 to 94%, in some cases as efficient as regular applications of fungicides including CBACs (Köhl et al. 2015). In Co-FREE, interesting results were obtained with applications of *Lysobacter capsici* AZ78 (Puopolo et al. 2014), as well as with formulated potassium bicarbonate product Armicarb and lime sulfur which reduced disease incidence and severity similar to or better than the copper hydroxide treatment when applied as stop sprays (Lukas et al. 2016). A plant-derived extract from *Larix decidua* bark has been developed in the ProLarix project which showed a good efficacy against downy mildew in grapevine (James et al. 2016). Its commercialization for control of downy mildew in grapevine is foreseen under the trade name Larixyne. In addition to control fungal diseases, products containing plant-based fatty acids have been evaluated for their ability to control bacterial diseases of dry beans which showed a higher level of effectiveness compared to CBACs under field conditions.

The application of biological control agents and plant extracts for substitution of CBACs replacement (Table 4) is under development, but not yet available for use by growers or registered only in a few countries. Further investments into development and registration of such agents remain to be done. In fact, only a few alternative crop protection products as broadly effective as Cu are available; thus, the replacement of CBACs with similarly functioning compounds continues to be a challenge. However, crop protection products with such broad spectrum activity will not be acceptable in future because of their general negative effect on biodiversity. The use of new selective crop protection products including biological control products will be compatible and complementary with practices which use and enhance disease suppression by the naturally preset microbiome which is often disturbed by broad spectrum fungicides including CBACs (van Lenteren et al. 2018). Future conscious agriculture with cropping systems relying on resilience against pests and diseases will thus need very selective crop protection products but not a replacement of broad CBACs by another group of broad spectrum compounds. Some effectiveness already shown by some of these compounds (Table 4), when combined with adequate cultural practices and accurate timing of applications, could potentially result in the replacement of CBACs in the near future.

6 Conclusions and perspectives

It is well known that CBACs are effective tools for crop disease management both in conventional and organic farming. However, reliance on these compounds, as the sole means of disease management, poses serious threats to sustainable agricultural production. The high level of Cu accumulation in the soil and the risk of surface and subsurface water contamination and potential public health problems due to Cu entering the food chain have raised concerns on the use of CBACs in agriculture. As a consequence, there is a worldwide community and regulatory pressure on agriculture in general, and in organic farming systems in particular, to restrict the use of these compounds (Wightwick et al. 2013). Therefore, an integrated program based on prevention and alternative practices—which would involve the re-design of cropping systems, with better management of soil fertility, irrigation, and with the proper combination of CBACs and new compounds or without any use of CBACs—should be developed for effective and sustainable crop disease management.

A significant reduction in the use or a complete replacement of CBACs in agriculture seems to be a major challenge at present. A limited number of sustainable alternatives is available on the market, and their uptake by farmers is still low due to the fact that CBACs are available at highly competitive prices. More restrictions in use of CBACs would foster the use of such already available alternatives. New initiatives may help achieve the objective of reducing reliance on CBACs. To this aim, besides focusing on resistant/tolerant cultivars which certainly is straightforward, we should investigate whether resilient cropping systems would allow reduced use of CBACs or complete elimination.

Another issue with CBACs is to develop improved application of low dosages of copper. Because the use of CBACs can be optimized, the application of these compounds needs to be reinforced by effective decision support systems taking into account most relevant biotic and abiotic factors that could influence their effectiveness. Investment in improved application technologies and timing will, in many cases, also improve the application of new alternative products and will thus reduce the reliance on copper. In addition, further development and registration of alternative substances to Cu should be encouraged since currently there are not enough valid alternatives to CBACs. Meanwhile, the relative risks of products developed as alternatives to Cu should be evaluated properly to ensure that they pose a lower environmental risk than CBACs they may replace.

Unlike problems related to resistance development by plant pathogenic strains which need an immediate solution to ensure sustainable crop production, it is not still clear as to the extent that CBACs pose a significant risk to soil and water biota. However, a number of reports in the literature indicate that continued applications of CBACs have implications on the use of those lands with high Cu levels for sustainable agricultural production. Because no standard tests are yet available to determine the toxicity of Cu for soil and water biota, such as those found in other fields of ecotoxicology, future studies should focus on the development of ecological risk assessment framework to precisely analyze the risks of Cu toward soil and water organisms and sustainable agriculture production.

Uncertainty in the prediction of impacts of external stressors including the application of CBACs on the agricultural ecosystem still represents a severe obstacle, and our knowledge on their long-term effects is still poor (Liess 2004). Therefore, questions can be raised on the short- and even long-term impact of Cu on soil biota population changes. This is especially true where no other indicator of harm due to Cu has been documented. Formulation of appropriate plans that could reduce the risks associated with Cu thus represents a key strategy in the near future, which might be a real challenge for policy makers globally.

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