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Julie Leclercq-Dransart, Sylvain Demuynck, Francis Douay, Fabien Grumiaux, Céline Pernin, Alain Leprêtre

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BISPHOSPHONATES FOR THE TREATMENT OF FIBROUS DYSPLASIA OF BONE

Roland Chapurlat¹, Mélanie A. Legrand¹

¹ INSERM UMR 1033, Université de Lyon, Hôpital E Herriot, Lyon cedex 03, France

roland.chapurlat@inserm.fr

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ABSTRACT

Introduction

Fibrous dysplasia of bone (FD) is a rare congenital bone disease, due to a somatic mutation of GNAS. This mutation **results** in a defect of osteoblast differentiation and mineralization and also an increase in bone resorption by large active osteoclasts. Bone pain is present in half of patients and is the main determinant of quality of life of patients with FD. Bisphosphonates are known to reduce bone pain and reduce the risk of fracture in patients with bone metastases or Paget's disease. Bisphosphonates may have similar effects in FD.

In this article, we have reviewed the therapeutic potential of bisphosphonates to reduce bone pain due to FD, improve bone strength and reduce the occurrence of fracture.

Material and methods

We have reviewed 234 articles examining the effect of bisphosphonates on FD/Mc Cune Albright Syndrome with no date limit, in Pubmed and selected the articles with highest quality of methodology.

Results

Pamidronate therapy significantly decreased bone pain and bone resorption (urinary NTX, urinary and serum CTX). Pamidronate may improve radiological lesions of FD patients (filling of osteolytic lesion and/or cortical thickening). This data with intravenous pamidronate, however, has been obtained from observational **studies** and no randomized controlled trial is available. Randomized placebo-controlled trials of oral bisphosphonates (alendronate or risedronate) have failed to demonstrate a significant decrease in bone pain over placebo. Several studies including one randomized controlled trial have shown an increase in bone mineral density (BMD) at FD sites with oral and intravenous bisphosphonate treatment. No effect on occurrence of fracture has been reported.

Conclusion

In conclusion, intravenous bisphosphonates may be proposed to treat persistent, moderate to severe bone pain of FD, e.g., according to the guidelines from the FD/MAS International Consortium. Oral bisphosphonates should not be used in this indication.

HIGHLIGHTS

- Intravenous bisphosphonates have been used in the treatment of fibrous dysplasia of bone for more than two decades, with data obtained in observational studies.
- Oral bisphosphonates are not recommended because their absence of efficacy has been demonstrated

INTRODUCTION

Fibrous dysplasia of bone (FD) is a rare bone disease due to a somatic mutation of GNAS (Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide) [1], so it is congenital but not hereditary. The replacement of normal bone by the proliferation of fibrous connective tissue with woven bone trabeculae is the main histologic characteristic [2]. The mutation of GNAS is responsible for a differentiation defect of stem cells into osteoblastic cells, leading to fibroblast-like cells, producing a poorly mineralized disorganized bone matrix. The clinical presentation of FD is heterogeneous: some patients will present with a mild if not asymptomatic form, diagnosis often being incidental, whereas some will present with severe impairment [3,4]. FD may either occur as an isolated bone condition or as part of the McCune-Albright syndrome (MAS), characterized by the following triad: FD, hyperfunctioning endocrinopathies, and/or café-au-lait spots [5].

Complications include fracture, bone pain, nerve compression (for instance with a risk of visual loss and hearing impairment), and endocrinopathies, such as peripheral precocious puberty, growth hormone hypersecretion, hyperthyroidism, and more rarely neonatal Cushing syndrome [6,7]. A sizeable number of patients have renal phosphate wasting because mutated cells produce excess amounts of the phosphate-regulating hormone fibroblast growth factor-23 (FGF23), leading to loss of phosphate in the urine [8]. Fibrous dysplasia is also associated with a variety of malignant conditions, including the bone sarcomatous transformation, pancreatic mucinous tumors, hepatic adenomas, thyroid cancer, and an increased risk of breast cancer [7,9–11]. Some patients are also affected by benign myxomas (Mazabraud syndrome) [12]. Quality of life is generally not impaired in those with limited FD, but decreased in those patients with polyostotic FD and MAS [13]. Bone pain is one of the determinants of the diminished quality of life. It is also observed in roughly the half of patients [4], and therefore is one of the most important targets of the potential medical therapies of the disease.

Even if FD is a disease of the osteoblastic lineage, the bone lesions are also surrounded by large active osteoclasts, digging tunnels reminiscent of those observed in hyperparathyroidism and probably contributing to the development of the osteolytic lesions of FD. Therefore, bisphosphonates may be active to treat this secondary aspect of the disease. Bisphosphonates have long been considered as potentially effective drugs to reduce bone pain in patients with skeletal complications of malignancies [14,15]. Alendronate has also been shown to reduce bone pain of type 1 complex regional pain syndrome [16] and Paget's disease of bone [17]. It has been suggested that alendronate may decrease bone pain by inhibiting bone resorption and inducing an anti-inflammatory effect [18]. It also been shown that bisphosphonates exert central and peripheral antinociceptive effects that may be mediated by extraskeletal mechanisms, such as inhibition of pro-inflammatory cytokines, neuropeptide Y and prostaglandins [19,20]. Thus, bisphosphonates may also reduce bone pain in FD, although no further specific research has been conducted on the potential mechanism of action of this drug family on bone pain.

As bisphosphonates - by their antiosteoclastic activity - have also been shown to allow for refilling osteolytic lesions of Paget's disease of bone and reduce the risk of fracture in patients with malignant bone disease, it has been postulated that they could also improve bone strength in FD.

In this article, we will review the therapeutic potential of bisphosphonates to alleviate bone pain due to FD and also the possibility that these drugs may improve bone strength and diminish the occurrence of fracture, along with effects on bone turnover.

METHODS

To identify the studies used in this narrative review, we have performed a PubMed search looking for articles examining the effect of bisphosphonates on FD/MAS, with no date limit up to the end of 2019. The search terms were fibrous dysplasia of bone, McCune-

Albright syndrome, bisphosphonates. This search produced 234 references. Then, we have selected articles considered of adequate quality, i.e., those reporting design and outcomes with sufficient detail (study design, methods to measure outcomes), cohort studies with the most important sample size (at least five patients) and randomized controlled trials. We could also make exceptions for case reports exhibiting meaningful examples. In this literature on a rare disease, however, the usual standards of quality used in systematic reviews and meta-analyses cannot be matched.

EFFECTS OF BISPHOSPHONATES ON BONE PAIN OF FIBROUS DYSPLASIA

We first address the effects on bone pain, in open and randomized studies, then the effect on bone structure, and finally the safety. The various therapeutic effects of bisphosphonates in FD/MAS are summarized in Table 1.

Open studies

The first attempts to use bisphosphonates in the treatment of FD were made in the 1990s. Intravenous pamidronate was chosen by analogy with the most potent regimen for treatment of Paget's disease of bone used at that time. The reasoning was that by targeting the increased bone resorption - a consequence, not a cause of the disease - bone pain and other adverse consequences of FD would be affected. Thus, in an open case series of only nine patients, striking radiographic improvements and decrease in bone pain and biochemical markers of bone remodeling were shown by Liens et al [21]. In this analysis, adult patients had received intravenous pamidronate (180 mg every 6 months). They were also supplemented with calcium (500–1500 mg/day) and vitamin D (800–1200 IU/day).

This regimen has been reassessed, with additional patients and longer follow-up, with similar results by Chapurlat et al [22, 23]. Children and adolescents - who represented 30% of this cohort - were also treated, with a dose of 3 mg/kg/treatment cycle. Pain intensity was assessed using a 0- to 4-point verbal pain scale. Fifty-eight patients have been treated with

intravenous pamidronate and followed up for an average of 50 months (ranging from 1 to 11 years). In this observational context, pain intensity has been significantly reduced by 41% in those patients on pamidronate, after the first course of treatment, with an additive effect (69% significant reduction) observed after several treatment cycles. Biochemical markers of bone turnover —such as total alkaline phosphatase, serum osteocalcin, and urinary type 1 collagen C-terminal breakdown products (CTX) were significantly reduced compared with baseline. There was no significant predictor of response to treatment, such as disease burden, age or level of bone turnover. Results were similar in adults and children or adolescents.

Favorable outcomes have also been observed in another non randomized open study by Parisi et al, using pamidronate, infused at 6-month intervals in 7 patients. Bone pain was significantly relieved and the level of bone turnover as assessed by biochemical markers was also reduced [24].

A few patients have also been treated successfully with other regimens. For example, in a 22-year-old woman who received four 90-mg infusions of pamidronate every 4 weeks, followed by oral alendronate 10 mg/day [25], a parallel relief in bone pain and decrease in urinary type 1 collagen N-terminal breakdown products (NTX) was obtained. In a series of six adult patients who have been treated with pamidronate followed by alendronate or used alendronate alone, Lane et al found that bone pain, evaluated using a visual analog scale ranging from 0 to 10, decreased substantially in response to therapy, bone resorption was reduced with intravenous pamidronate but not with oral alendronate [26]. In a series of 30 patients with polyostotic FD, Majoor et al observed that 80% of patients benefited from a complete response to olpadronate, administered mostly IV, but also orally [27]. All other patients tended to exhibit a lower level of bone pain, but without complete resolution.

Although bone pain declined substantially in most patients exposed to pamidronate therapy, a subset (15% in our experience) did not exhibit any improvement in bone pain.

Some other patients, despite an initial positive response to treatment, suffer from a relapse in bone pain. In this context, we have treated 9 patients who had been on pamidronate were switched to zoledronic acid, because they had relapsed bone pain and/or increased levels of biochemical markers of bone turnover [28]. Zoledronate 4 mg was administered intravenously every 6 months, along with calcium and vitamin D supplements (oral calcitriol and phosphorus was added in those with renal phosphate wasting). The mean age of these six women and three men who had been on pamidronate for 9 years on average (range, 0.5–16 years) before starting zoledronic acid was 39 years (range, 22–63 years). All patients had polyostotic FD.

Among the five patients who had bone pain when they started zoledronic acid, the mean pain score tended to be reduced by 60% ($p = 0.09$). Serum CTX decreased by 24% ($p = 0.23$), but total serum alkaline phosphatase (0%, $p = 0.50$) and serum osteocalcin (0%, $p = 0.32$) did not change.

Randomized placebo-controlled trials

Based on the observational data and on the fact that an oral drug would improve patient comfort, the value of oral alendronate has been tested in a placebo-controlled randomized trial [29]. With the same premise that in the initial observational studies of IV drugs, the higher Paget's disease of bone dosage has been chosen. Therefore, 40 patients with polyostotic FD were randomized in a single American center to receive either alendronate daily or placebo, over 24 months. Adults were on 40 mg daily for 6 months, followed by 6 months off drug and this cycle was repeated once; children received a lower dose, adapted to their body weight. The primary endpoint was the variation in urinary NTX, whereas bone pain was analyzed as a secondary outcome, in an intent-to-treat analysis at 18 months. The urinary NTX was significantly decreased, but the bone pain did not decline. Of note, those patients

were not selected based on bone pain and their baseline level of bone pain was moderate, at 3 out of 10, which might explain the inability to decrease it further.

Another oral bisphosphonate - oral risedronate - has been tested in a randomized setting, the PROFIDYS trial. In this multicenter European trial, 41 patients were randomized to take risedronate 30 mg/day or a matching placebo for 2 months, followed by a 4 months off-therapy period, and this cycle was repeated once. Patients were selected based on their level of bone pain, which was on average at 5.7/10 at the baseline. [The full publication has not been released yet, but the decline in bone pain at one year in the risedronate group was superimposable to that of the placebo group \[personal oral communication\].](#)

EFFECTS OF BISPHOSPHONATES ON BONE STRUCTURE OF FIBROUS DYSPLASIA

In the largest and most prolonged observational studies of intravenous pamidronate [19, 20], one half of those treated patients had discernible radiological improvement, characterized by filling of osteolytic lesion and/or cortical thickening. This finding, however, was not universal, as shown in a pediatric study from Canada [30]. When measurements were repeated over time in patients who had hip involvement, total hip BMD was substantially increased on pamidronate [23,25]. Also, in seven adult patients with various forms of FD treated with intravenous pamidronate, the mean BMD in affected areas was increased by 6.8% compared with an increase of 2.6% in unaffected areas after 1 year of treatment [24]. No obvious change was observed on plain radiographs, suggesting that BMD measurements were more sensitive to detect bisphosphonates effects on the dysplastic bone, at least over this short period of follow-up. With zoledronate, no significant change in radiological aspect was reported [28].

In the randomized trial of alendronate, no change in imaging aspect of bone density was obtained [29]. The imaging results of the PROFIDYS Trial of risedronate - over 3 years of follow-up - have not been reported yet.

The influence of these imaging changes associated with bisphosphonate use of the risk of fracture have not been evaluated prospectively.

Based on the results reported here, a clinical guideline has been published recently by the FD/MAS International Consortium, supporting the use of this therapeutic class (summarized in Table 3).

SAFETY OF BISPHOSPHONATES IN THE TREATMENT OF FIBROUS DYSPLASIA

The side effects of bisphosphonates in FD/MAS are summarized in Table 2. No concern specific of FD regarding safety of bisphosphonates in the treatment of FD has emerged. Transient fever was observed in roughly a third of patients, generally only after the first infusion of IV bisphosphonates. Few patients developed venous irritation after slow pamidronate infusion. After three courses of pamidronate, a 14-year-old MAS patient presented with mineralization defects, in a context of renal phosphate wasting [22]. In the only study with extensive histomorphometric analysis, no patient fulfilled the histomorphometric criteria for osteomalacia in unaffected bone, but this analysis was conducted in children and adolescents, with no adult patients involved [30].

Osteonecrosis of the jaw is a potential complication of bisphosphonate use. An incidence of 5.4% has been reported in a series of 76 patients who had received a high cumulative dose of IV bisphosphonates [31]. No pediatric patient with osteonecrosis of the jaw has been reported.

Two cases of ocular inflammation were described with Pamidronate [24]. This side effect has been previously reported with BP in other diseases [32]. A few cases of hypocalcemia with IV bisphosphonates have been described [21].

No atypical fracture of the femoral diaphysis - reminiscent of those observed in patients treated with bisphosphonates for osteoporosis - has been described.

DISCUSSION

Two randomized trials of oral bisphosphonates have failed to demonstrate a significant decrease in bone pain over placebo. Therefore, those two drugs - alendronate and risedronate - should not be used in this indication. The body of evidence regarding IV bisphosphonates has been obtained from observational studies. We cannot determine whether the decline in bone pain in open studies was purely in relation with the placebo effect and regression to the mean, or whether these other agents have a more important effect on bone pain that may be due to their different structure and potency. A few randomized placebo-controlled trials have shown that intravenous bisphosphonates can reduce bone pain more than placebo in a variety of other diseases affecting bone [33–36], including a trial showing superiority of intravenous zoledronate over oral risedronate in Paget's disease of bone [37]. In addition, the doses of IV bisphosphonates that were used in most observational studies could possibly be increased to obtain a better response. Indeed, the decrease in bone pain observed after a first infusion of pamidronate is roughly 40% [22], which is comparable to the placebo response in the risedronate randomized trial. Nevertheless, the subsequent infusions allowed for an average reduction of about 70% [22,23], suggesting an additive effect of a greater cumulative dose. A greater nominal reduction in bone pain of 60% was also obtained with zoledronate [28], which is a more potent compound than pamidronate, that was also more effective in trials of prevention of skeletal events of bone malignancies [14]. With olpadronate, repeated doses also permitted a complete pain response in 80% of patients [27]. Greater cumulative doses

may also be associated with more side effects, such as osteonecrosis of the jaw. The potentially better efficacy of higher doses or of zoledronate has to be balanced with this safety concern. An increase in dose might be proposed only in those who fail to achieve a decline in pain greater than 50-60% after a first injection.

Some mechanisms involved in the generation of bone pain may account for the effect of bisphosphonates to treat bone pain, including that due to FD. Thus, it has been shown that osteoclast-induced acidosis may drive bone pain. Some sensory nerve fibers express acid sensing ion channels including TRPV1, ASIC1 and ASIC3 [38]. These receptors can be activated by pHs ranging from 3 to 4, which is the extracellular pH produced by osteoclasts while resorbing bone. As bisphosphonates induce osteoclastic apoptosis, the acidification does not occur with these drugs.

The use of biochemical markers of bone turnover has been advocated to identify responders to bisphosphonate therapy in FD and also to be a target of the treatment to determine the dose and duration of therapy [27]. In this study, however, the bone pain response was not correlated to the level of biochemical markers of bone turnover. Similarly, in other analyses [22,23], markers were not predictive of the bone pain response. This absence of association between biochemical markers of bone turnover and bone pain is also supported by the inverse relationship between the decline of their levels with age and the increase in pain intensity with ageing [39].

As a matter of good clinical practice, before starting IV bisphosphonate therapy, one should ensure that the patient is normocalcemic, the 25OHD level and the renal function are adequate. Renal phosphate wasting should be treated for at least several months before bisphosphonates are used. Dental evaluation is recommended, before the treatment initiation, in order to decrease the risk of osteonecrosis of the jaw.

The clinical research on FD and its treatment remains very active, but it is unlikely that new studies on the value of bisphosphonates be conducted. **Other potential targets, such as** interleukin-6, RANK-L and nerve growth factor, are more likely possibilities.

In conclusion, intravenous bisphosphonates may be proposed for persistent, moderate to severe bone pain of FD, as stated in the recent best practice management guidelines from the International FD/MAS International consortium [40]. Oral bisphosphonates, at any dose, are therefore not recommended for the treatment of bone pain. Intravenously administered pamidronate and zoledronate can be equally considered – Table 3. The dosages and dosing intervals should be determined according to the need for analgesia and the response to prior doses.

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TABLE TITLES

Table 1 – Effect of bisphosphonates treatment in FD, from literature review

Table 2 - Side effects reported in literature with [bisphosphonates](#) in treatment of FD

Table 3 – Intravenous [bisphosphonates](#) regimens proposed by FD/MAS international consortium for the management of bone pain in patients with FD/MAS



F1 : Mix plantation

Robinia pseudoacacia, *Salix alba*, *Acer pseudoplatanus*, *Alnus glutinosa*, *Quercus rober* distributed according to a regular cheme

Plantation in 2000
Mineral amendemant
(Alumino silicate fly ashes)
Inter-row distance: 2 m

Plot with ecological potential



M: 3 rows of maple trees

Plantation in 1998
No mineral amendement
Inter-row distance: 2 m

Plot with ecological potential

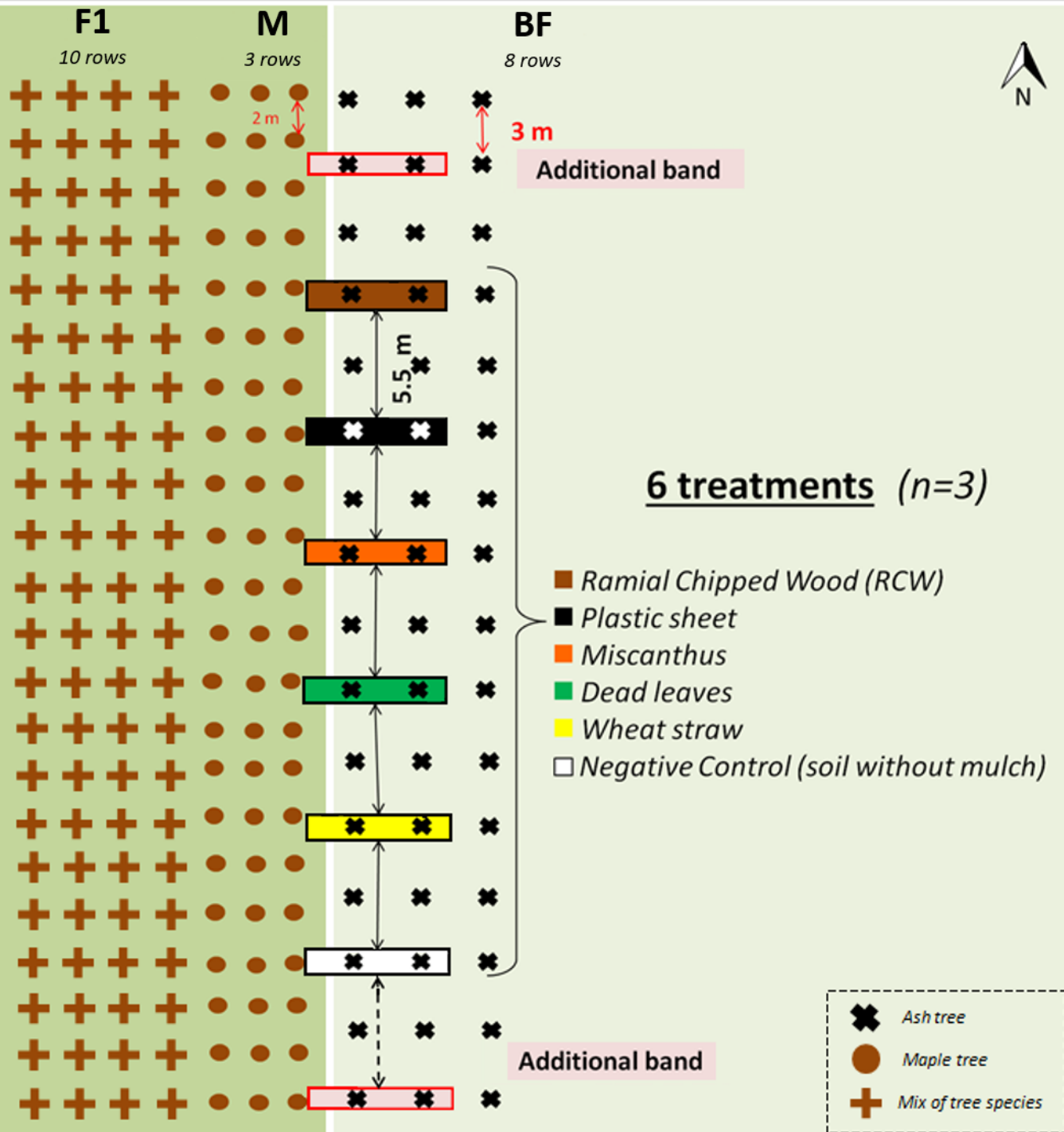


BF: Mono specific plantation (*Fraxinus sp*)

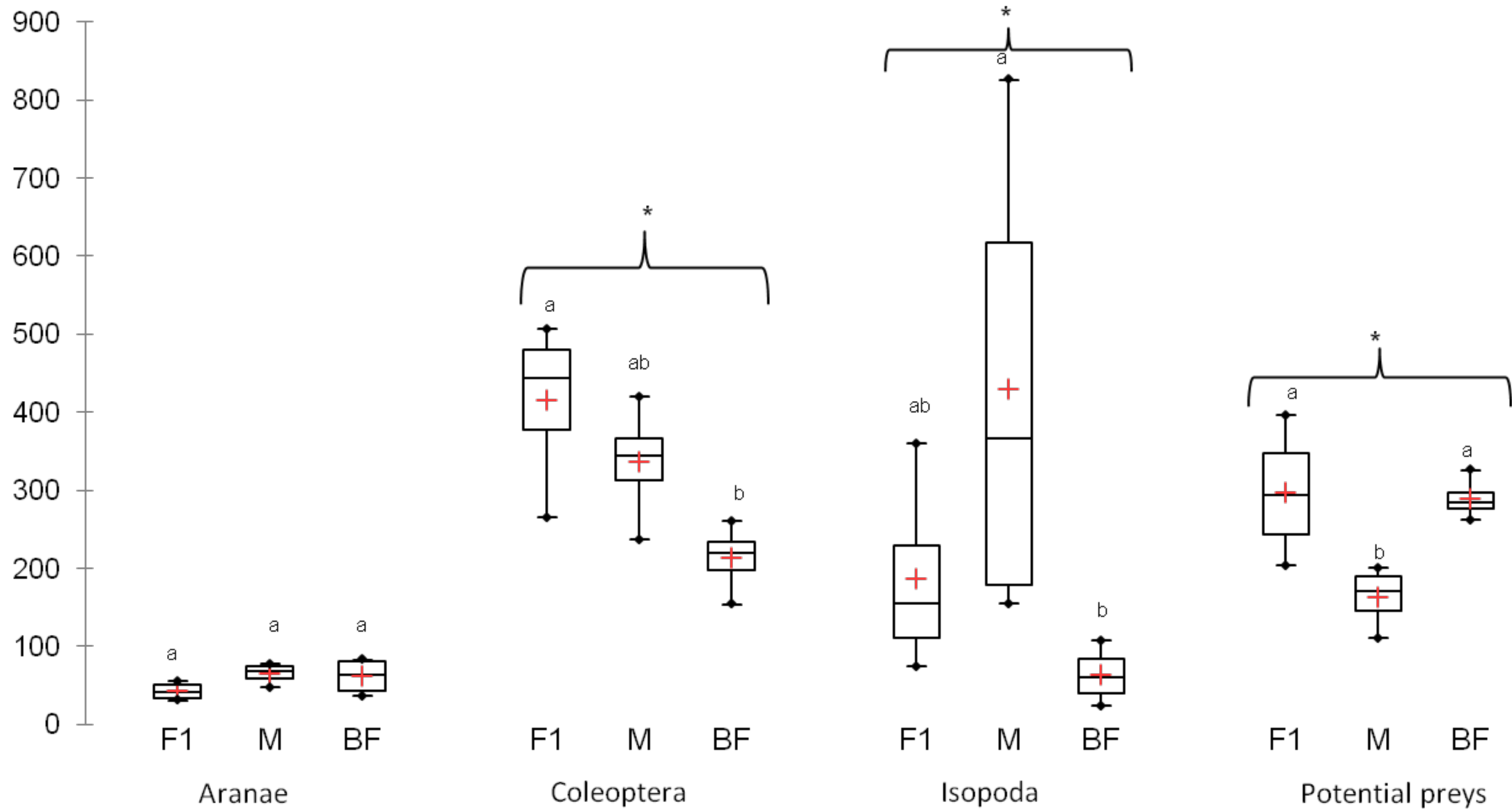
Plantation in 1997
No mineral amendement
Inter-row distance: 3m

Area to be restored

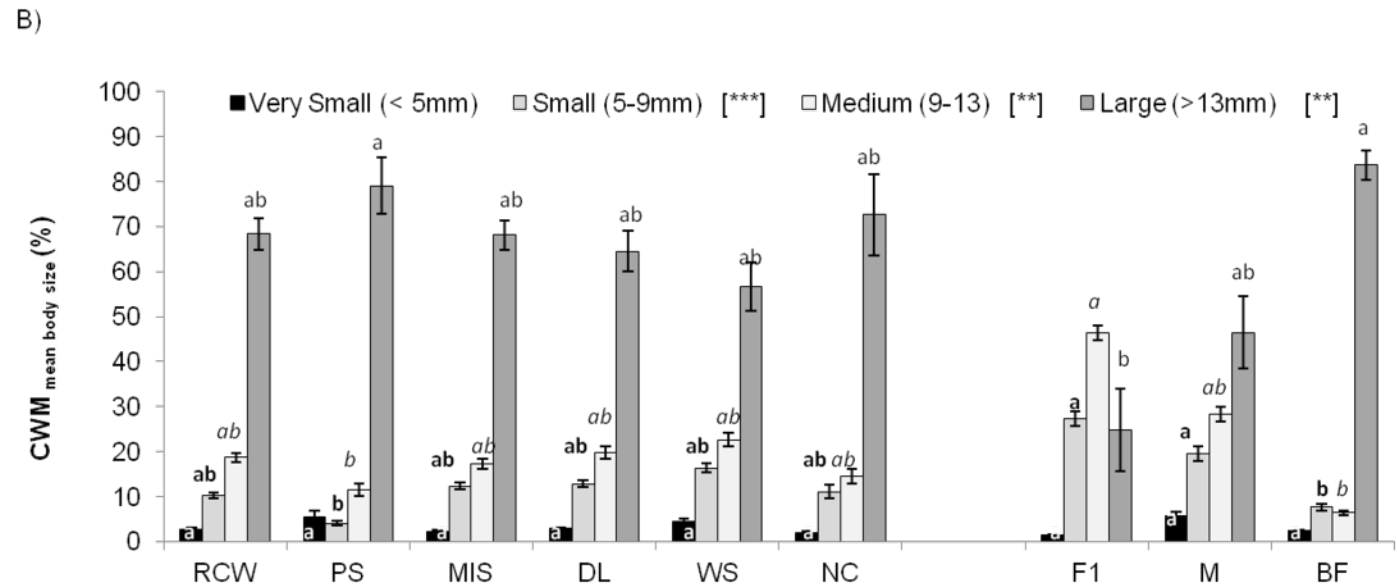
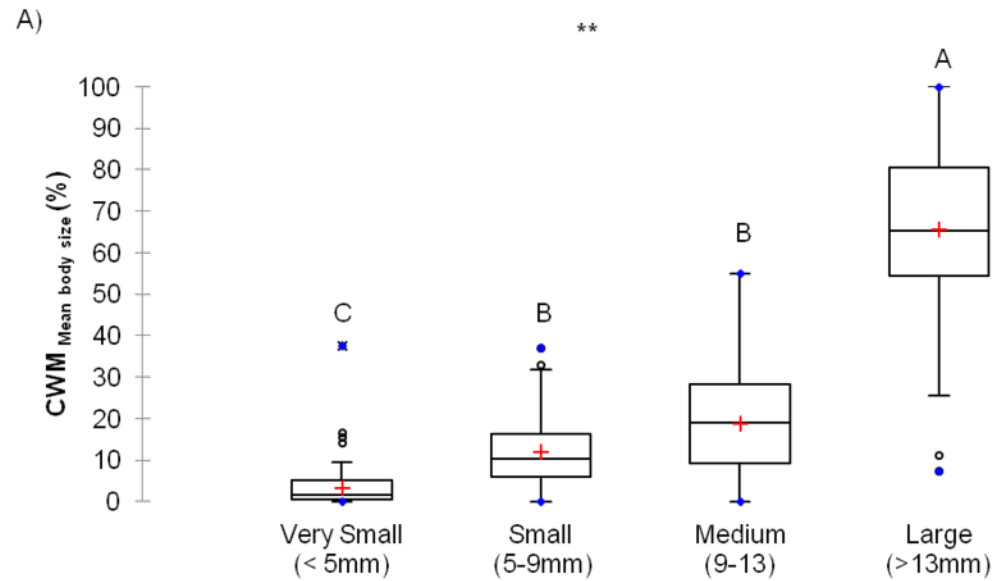




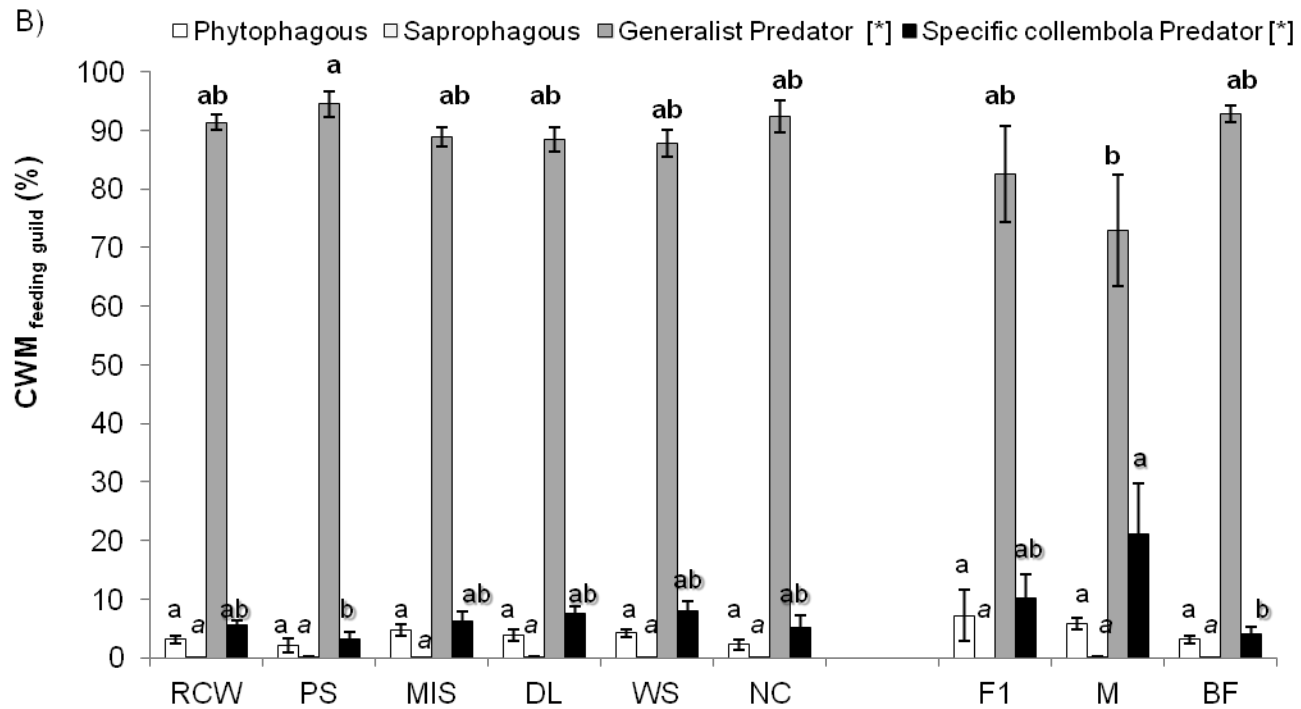
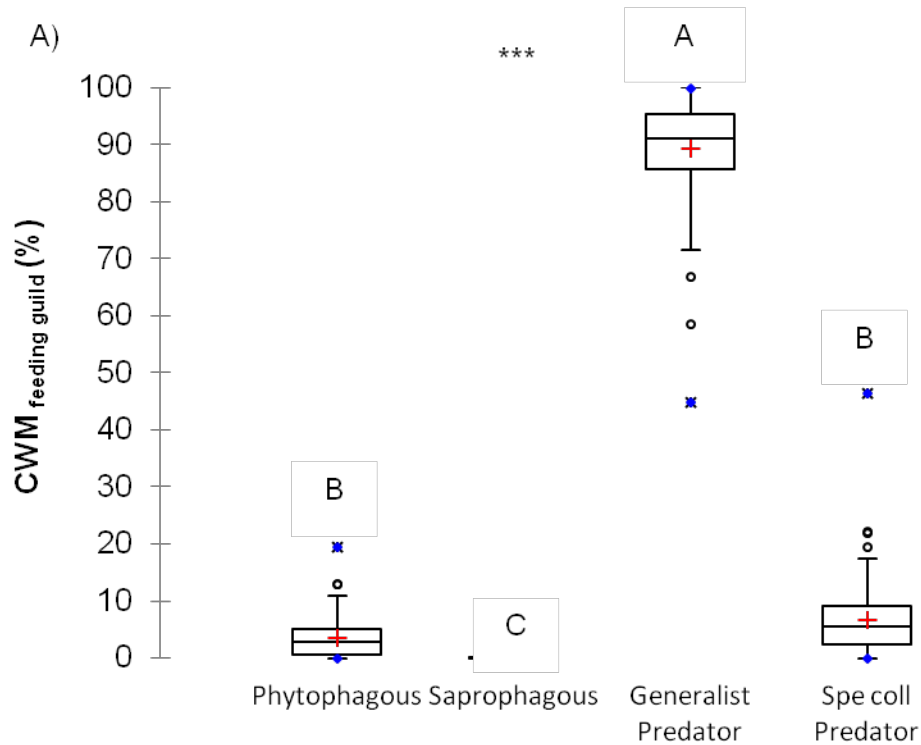
Total abundance (*individuals*)



1) Mean body size of adults

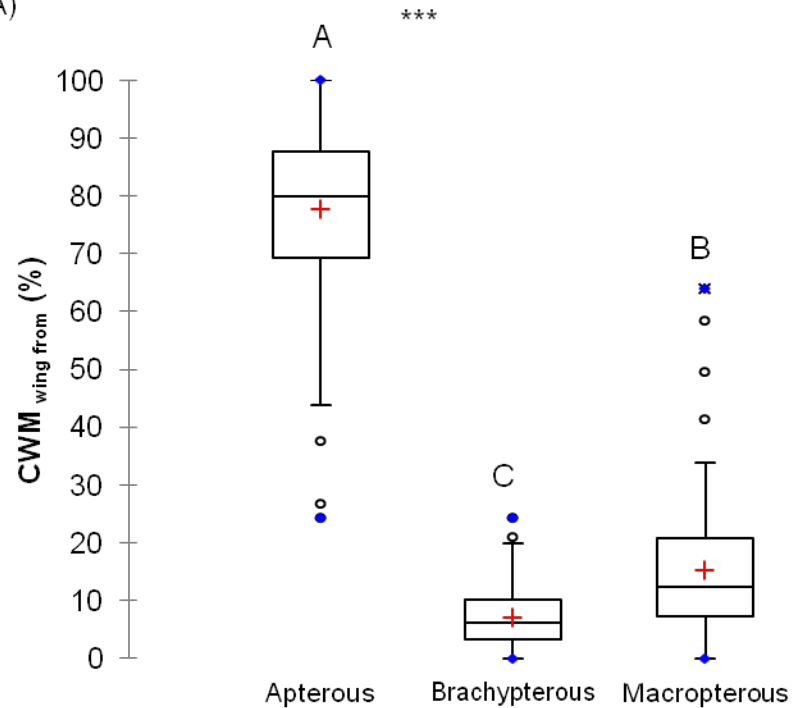


2) Feeding guild of adults

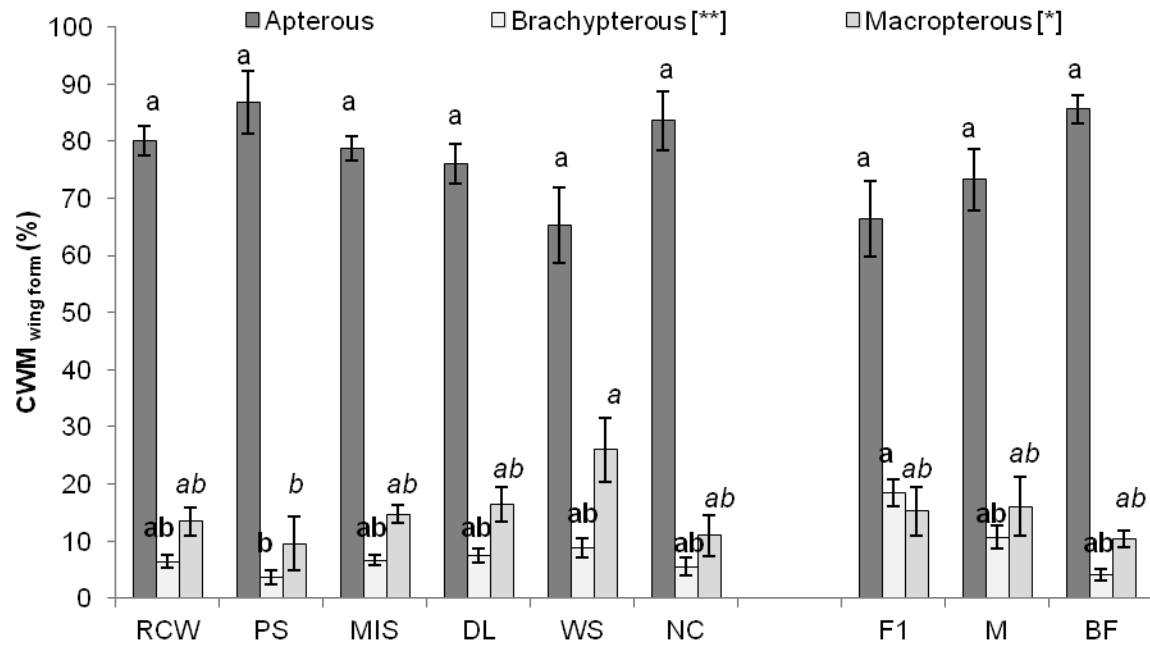


3) Wing form

A)

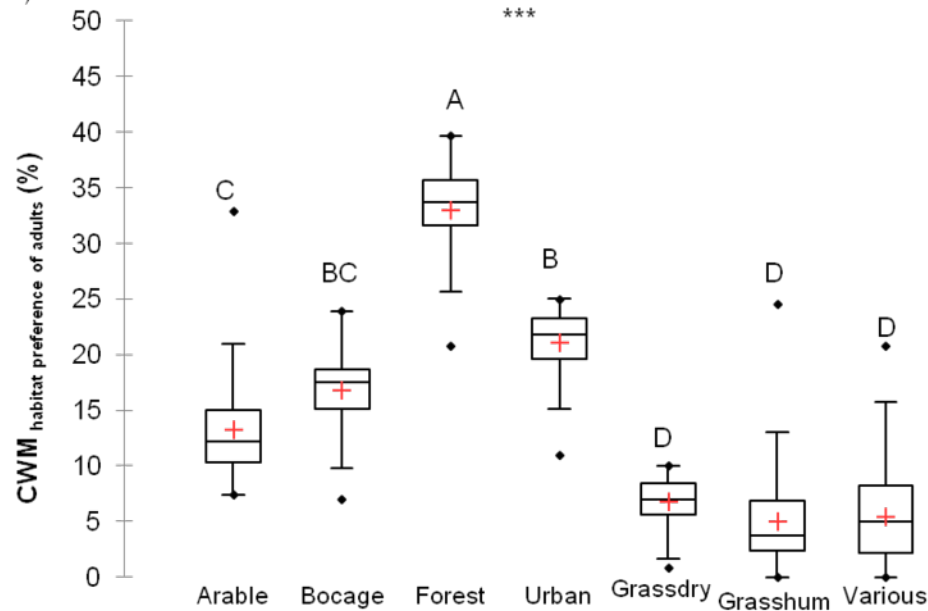


B)

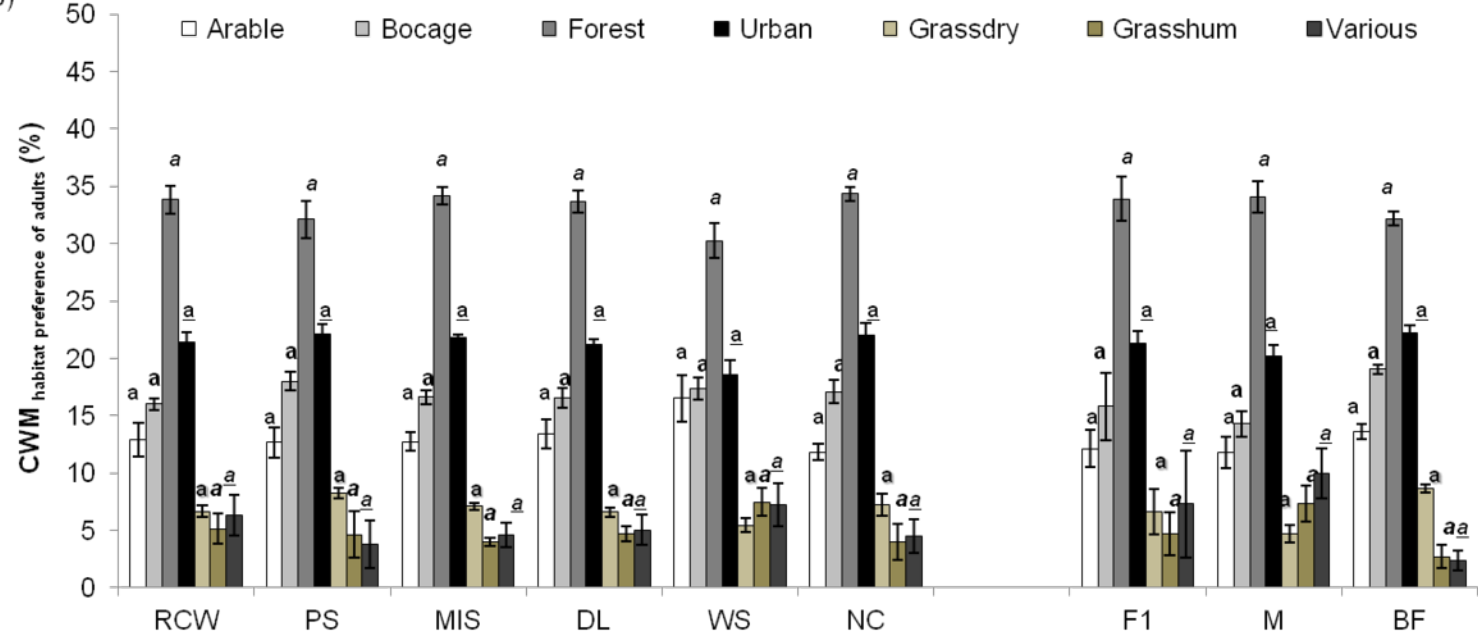


4) Habitat preference of adults

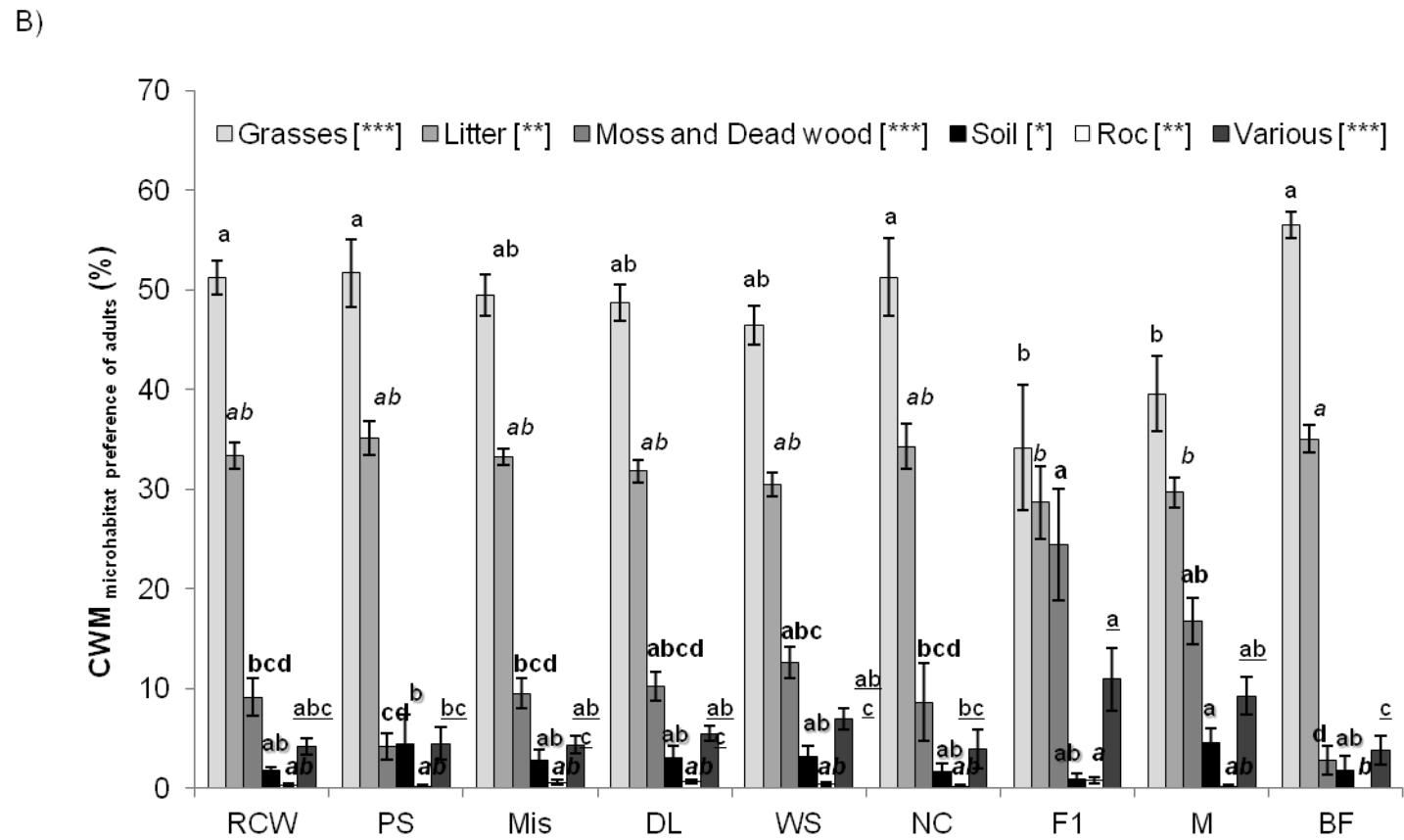
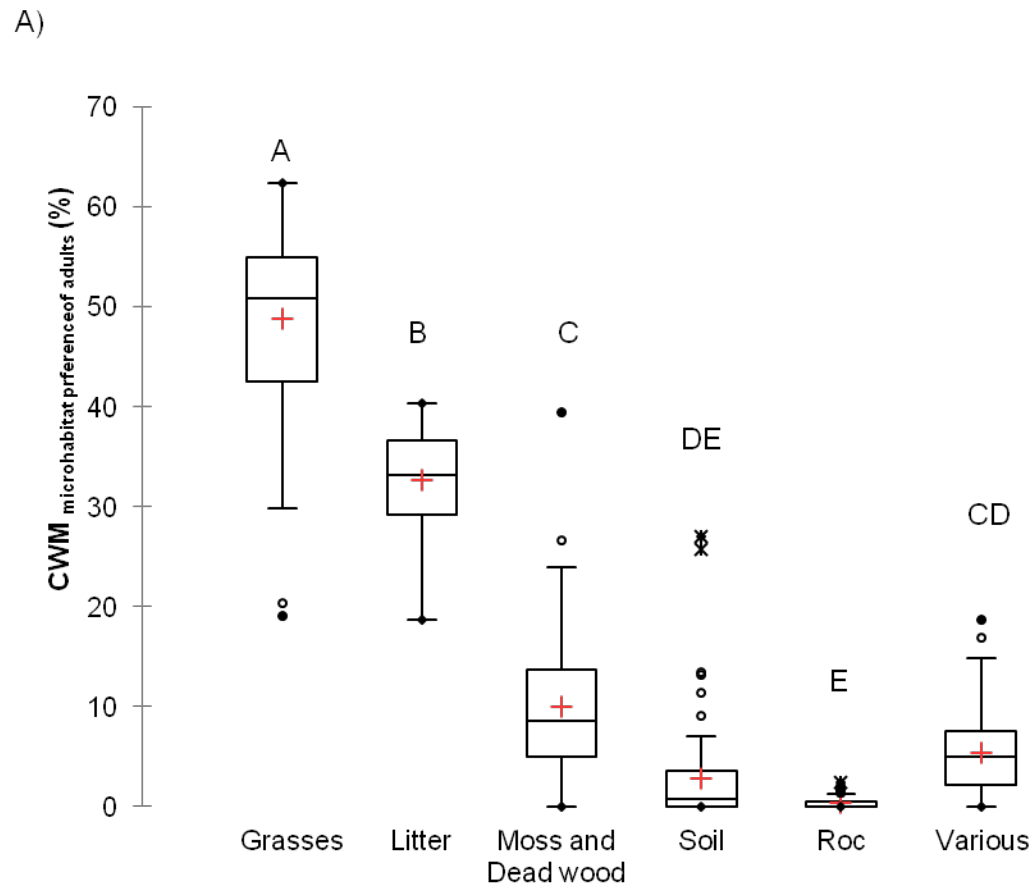
A)



B)



5) Microhabitat preference of adults



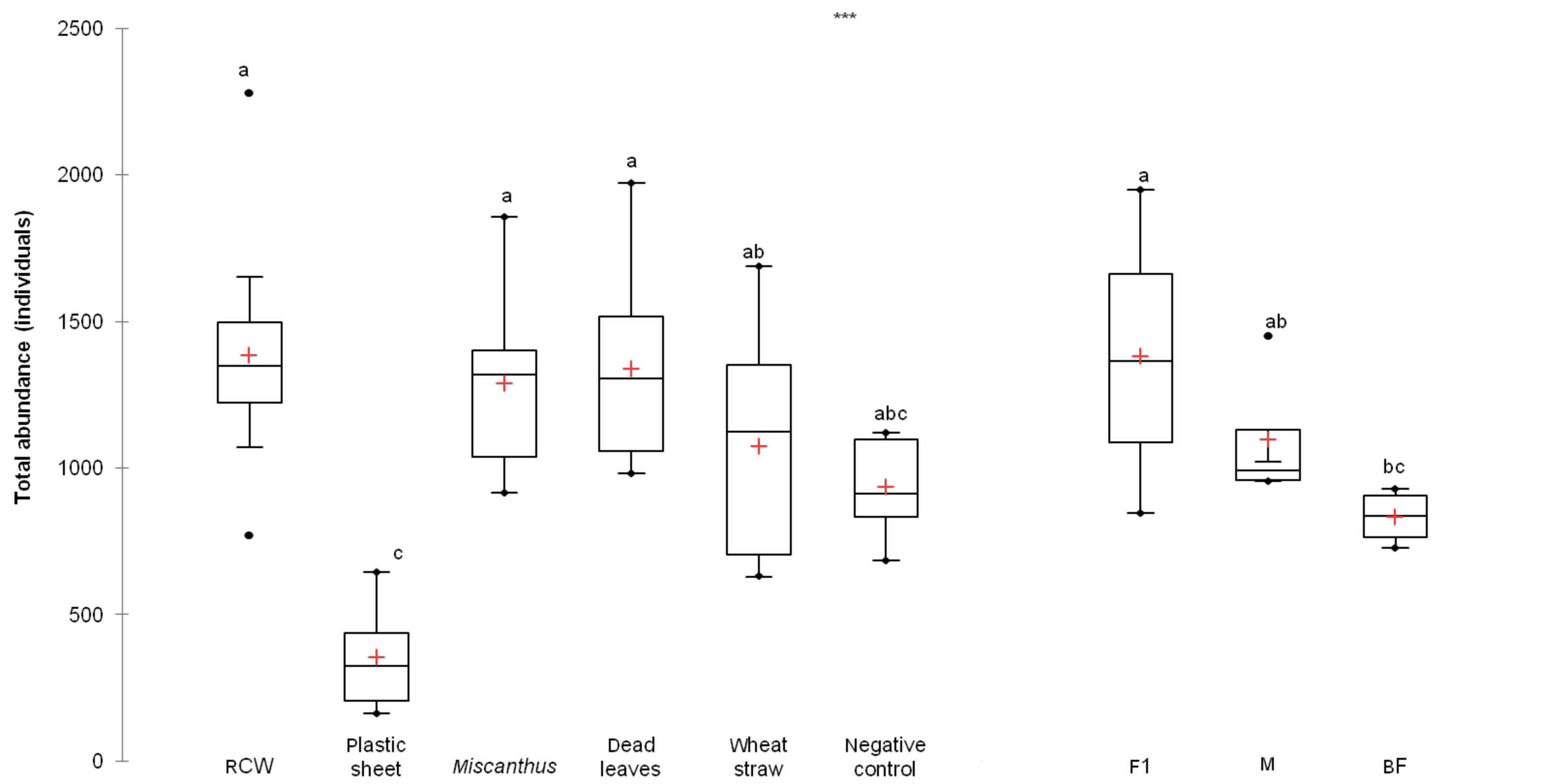


Table 1: Description and attributes of morphological, behavioural and physiological traits considered for the trait-based approach of the carabids community according to the Thesaurus for Soil Invertebrate Trait-based Approaches (Pey et al, 2014a) of BETSI data base (Biological and Ecological functional Traits of Soil Invertebrates – CESAB/FRB: <http://betsi.cesab.org/>) and several reference works (Dajoz, 2002; Jeannel, 1942, 1941; Laroche, 1990, Lindroth, 1974, Luff, 1998).

Traits	Attributes
Mean body size of individuals	Very small <5 mm Small 5-9 mm Medium 9-13 mm Large >13 mm
Feeding guild of adults	Generalist predator Collembola specialist Phytophagous Saprophagous
Wing form	Apterous Macropterous Brachypterous
Body reflection	Shiny Matt Metallic
Circadian activity rhythm	Nocturn Diurn Cathemeral Crepuscular
Habitat preference of adults	Arable Bocage Forest Urban (<i>urban green area : gardens, parks, herbaceous wastelands</i>) Grassdry Grasshum <i>Various (<5% of community : indust, inland, coastal and wetland)</i>
Microhabitat preference of adults	Grasses Litter Moss Dead wood Soil Roc (<i>pebbles, stones</i>) <i>Various (<5% of community : chalk, clay, no veg, sand, soil, solS, detrit, moss, nest)</i>

Table 2: Community parameters in the F1, M and BF plots adjacent to the experimental design.

a) Isopoda

	Test / p values	Pr > F	F1 plot	M plot	BF plot
Total abundance (individuals caught in the 6 traps during the 8 surveys)			744	1.715	251
Mean abundance per trap (individuals) ± SD	Kruskal Wallis	0.030	186 ± 125 (ab)	429 ± 319 (a)	63 ± 37 (b)
Total species Richness			5	6	5
Mean Species Richness ± SD	Kruskal Wallis	0.468	5 ± 1 (a)	5 ± 1 (a)	4 ± 1 (a)
Dominance_D ± SD	ANOVA F= 9.368	0.006	0.56 ± 0.09 (ab)	0.66 ± 0.09 (a)	0.42 ± 0.05 (b)
Simpson_1-D ± SD	ANOVA F= 9.368	0.006	0.44 ± 0.09 (ab)	0.34 ± 0.09 (b)	0.58 ± 0.05 (a)
Shannon_H ± SD	ANOVA F= 6.443	0.018	0.84 ± 0.14 (ab)	0.69 ± 0.14 (b)	1.03 ± 0.12 (a)
Evenness_J (Pielou's evenness) ± SD	ANOVA F= 11.956	0.003	0.56 ± 0.09 (b)	0.46 ± 0.11 (b)	0.76 ± 0.05 (a)

b) Carabidae

	Test / p values	Pr > F	F1 plot	M plot	BF plot
Total abundance (individuals caught in the 6 traps during the 8 surveys)			221	236	210
Mean abundance per trap (individuals) ± SD	ANOVA F= 0.146	0.867	55 ± 21 (a)	59 ± 14 (a)	43 ± 15 (a)
Total species Richness			18	20	20
Mean Species Richness ± SD	ANOVA F= 4.323	0.048	12 ± 2 (a)	11 ± 2 (a)	8 ± 2 (a)
Dominance_D ± SD	ANOVA F= 14.356	0.002	0.29 ± 0.05 (b)	0.29 ± 0.14 (b)	0.65 ± 0.12 (a)
Simpson_1-D ± SD	ANOVA F= 14.357	0.002	0.71 ± 0.05 (a)	0.71 ± 0.14 (a)	0.35 ± 0.12 (b)
Shannon_H ± SD	ANOVA F=4.685	0.004	1.69 ± 0.21 (a)	1.69 ± 0.38 (a)	0.32 ± 0.09 (b)
Evenness_J (Pielou's evenness) ± SD	ANOVA F= 8.562	0.008	0.69 ± 0.04 (a)	0.70 ± 0.13 (a)	0.42 ± 0.13 (b)

Different letters indicates statistical significant difference (ANOVA test followed by post-hoc Tukey's pairwise comparison test or Kruskal-Wallis test followed by post-hoc Dunn's pairwise comparison test).

Table 3: Abundance of the 42 species of carabids recorded in 2014 on and around the experimental system (n= 12 traps per modality for a total of 90 traps installed from April to July 2014)

	Ramial Chipped Wood (RCW)	Plastic sheet	<i>Miscanthus</i>	Dead Leaves	Wheat straw	Negative control	F1	M	BF	Total
<i>Abax parallelepepidus</i>	0	1	1	0	0	0	0	0	0	2
<i>Abax parralelus</i>	0	0	0	1	0	1	0	0	0	2
<i>Agonum afrum</i>	0	0	0	0	1	0	1	0	0	2
<i>Agonum nigrum</i>	0	0	0	0	0	0	0	1	0	1
<i>Amara aenea</i>	1	0	2	1	1	0	0	0	2	7
<i>Amara communis</i>	7	0	10	7	3	3	3	0	3	36
<i>Amara consularis</i>	0	0	0	1	0	0	0	0	0	1
<i>Anchomenus dorsalis</i>	0	0	0	0	1	0	0	0	0	1
<i>Anisodactylus binotatus</i>	1	0	1	2	0	0	0	0	0	4
<i>Asaphidion flavipes</i>	0	4	0	0	4	1	0	4	0	13
<i>Badister bullatus</i>	3	0	3	8	4	5	3	2	2	30
<i>Badister unipustulatus</i>	5	0	3	5	4	2	6	0	1	26
<i>Calathus rotundicollis</i>	70	14	51	80	53	29	92	50	3	442
<i>Carabus coriaceus</i>	1	0	0	0	0	0	0	0	0	1
<i>Harpalus affinis</i>	4	1	3	1	2	1	0	1	1	14
<i>Leistus ferrugineus</i>	3	3	5	5	6	2	8	17	0	49
<i>Lesitus spinibarbis</i>	30	4	27	38	35	15	19	16	2	186
<i>Loricera pilicornis</i>	0	1	2	1	4	0	0	0	0	8
<i>Metallina lampros</i>	3	3	5	7	5	1	0	2	2	28
<i>Nebria brevicollis</i>	32	2	31	38	47	10	4	12	1	177
<i>Nebria salina</i>	1	1	3	2	2	1	0	0	1	11
<i>(Nebria immature)</i>	3	0	7	2	3	1	2	1	2	21
<i>Notiophilus biguttatus</i>	15	0	17	9	7	5	1	9	1	64
<i>Notiophilus palustris</i>	5	1	2	11	3	1	1	1	4	29
<i>Notiophilus quadripunctatus</i>	0	0	0	2	0	0	0	0	0	2
<i>Notiophilus rufipes</i>	2	0	2	0	0	0	0	0	0	4
<i>Notiophilus substriatus</i>	1	0	1	1	0	1	2	1	1	8
<i>Ocydromus femoratus</i>	1	0	0	1	1	0	0	0	1	4
<i>Ophonus subquadratus</i>	0	0	0	1	0	0	0	0	0	1
<i>Oxypselaphus obscurus</i>	1	0	0	0	0	0	3	0	0	4
<i>Paranchus albipes</i>	0	0	0	2	1	1	0	0	0	4
<i>Philochthus guttula</i>	1	0	0	1	3	0	0	0	0	5
<i>Poecilus versicolor</i>	3	2	3	3	6	1	0	1	1	20
<i>Pseudoophonus rufipes</i>	2	0	0	0	3	1	3	2	1	12
<i>Pterostichus macer</i>	5	3	1	1	1	0	0	2	1	14
<i>Pterostichus madidus</i>	475	163	385	431	323	326	55	107	170	2435
<i>Pterostichus melanarius</i>	31	1	13	19	28	9	3	1	9	114
<i>Pterostichus nigrita</i>	0	0	2	0	3	0	0	0	0	5
<i>Pterostichus strenuus</i>	2	0	3	7	12	4	10	3	1	42
<i>Pterostichus vernalis</i>	0	0	1	1	4	1	2	0	0	9
<i>Stomis pumicatus</i>	5	1	6	5	1	1	3	0	0	22
<i>Synuchus vivalis</i>	0	0	0	0	1	0	0	1	0	2

<i>Trechus quadristriatus</i>	0	1	3	1	2	0	0	2	0	9
Abundance	713	206	593	695	574	423	221	236	210	3871
Species richness	27	17	27	31	31	23	18	20	20	42

Table 4: Community parameters under the mulches and control

a) Carabids

	Test / p values	Pr > F	RCW	Plastic Sheet	<i>Miscanthus</i>	Dead leaves	Wheat straw	Negative control
Total abundance (individuals caught in the 12 traps during the 8 surveys)			713	206	593	695	574	423
Mean abundance per trap (individuals) ± SD	ANOVA F= 5.915	0.00016	59 ± 19 (a)	17 ± 10 (b)	49 ± 21 (a)	58 ± 27 (a)	48 ± 25 (a)	53 ± 27 (a)
Total species Richness			27	17	27	31	31	23
Mean Species Richness ± SD	Kruskal Wallis	<0.0001	9 ± 3 (a)	3 ± 2 (b)	9 ± 3 (a)	10 ± 3 (a)	10 ± 2 (a)	8 ± 3 (ab)
Dominance_D ± SD	Kruskal Wallis	0.047	0.478 ± 0.165 (ab)	0.680 ± 0.293 (a)	0.456 ± 0.129 (ab)	0.435 ± 0.176 (ab)	0.358 ± 0.145 (b)	0.580 ± 0.298 (ab)
Simpson_1-D ± SD	Kruskal Wallis	0.047	0.522 ± 0.165 (ab)	0.320 ± 0.293 (b)	0.544 ± 0.129 (ab)	0.565 ± 0.176 (ab)	0.642 ± 0.145 (a)	0.420 ± 0.298 (ab)
Shannon_H ± SD	ANOVA F= 5.229	0.00045	1.191 ± 0.377 (a)	0.621 ± 0.592 (b)	1.256 ± 0.298 (a)	1.326 ± 0.417 (a)	1.527 ± 0.377 (a)	1.020 ± 0.724 (ab)
Evenness J (Pielou's evenness) ± SD	ANOVA F= 1.288	0.28	0.549 ± 0.139 (a)	0.634 ± 0.245 (a)	0.594 ± 0.115(a)	0.590 ± 0.158 (a)	0.670 ± 0.149 (a)	0.488 ± 0.267 (a)

b) Isopods

	ANOVA / p value	RCW	Plastic Sheet	<i>Miscanthus</i>	Dead leaves	Wheat straw	Negative control
Total abundance (individuals caught in the 12 traps during the 8 surveys)		6325	951	5204	5873	3603	1196
Mean abundance per trap (individuals) ± SD	p<0.0001	527 ± 320 (a)	79 ± 91 (c)	434 ± 313 (ab)	489 ± 344 (ab)	300 ± 253 (abc)	150 ± 86 (bc)
Total species Richness		6	6	6	6	6	5
Mean species Richness ± SD	p=0.01	4.67 ± 0.778 (ab)	4.5 ± 0.905 (b)	5.08 ± 0.515 (ab)	5.42 ± 0.515 (a)	4.5 ± 1.31 (ab)	4.5 ± 0.535 (b)
Dominance_D ± SD	p=0.002	0.797 ± 0.155 (a)	0.492 ± 0.219 (b)	0.723 ± 0.182 (ab)	0.784 ± 0.168 (a)	0.725 ± 0.164 (ab)	0.650 ± 0.123 (ab)
Simpson_1-D ± SD	p=0.002	0.203 ± 0.155 (b)	0.508 ± 0.219 (a)	0.277 ± 0.182 (ab)	0.216 ± 0.168 (b)	0.275 ± 0.164 (ab)	0.350 ± 0.123 (ab)
Shannon_H ± SD	p=0.002	0.432 ± 0.261 (b)	0.980 ± 0.40 (a)	0.583 ± 0.320 (ab)	0.467 ± 0.278 (b)	0.568 ± 0.306 (ab)	0.707 ± 0.217 (ab)
Evenness_J (Pielou's evenness) ± SD	p=0.001	0.293 ± 0.194 (b)	0.667 ± 0.250 (a)	0.366 ± 0.229 (b)	0.283 ± 0.177 (b)	0.380 ± 0.158 (ab)	0.474 ± 0.147 (ab)

Different letters indicates statistical significant difference (ANOVA test followed by post-hoc Tukey's pairwise comparison test or Kruskal-Wallis test followed by post-hoc Dunn's pairwise comparison test).

