



Trace metals with heavy consequences on bees: A comprehensive review

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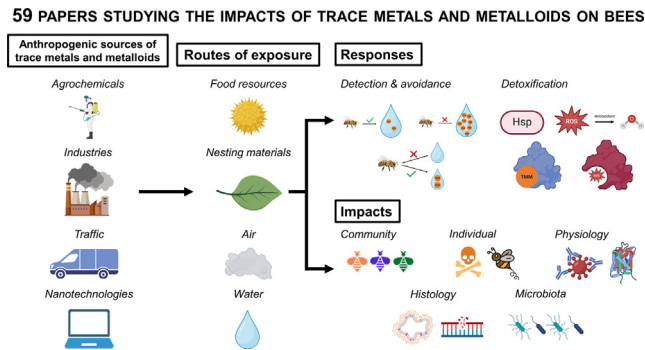
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HIGHLIGHTS

- Bee populations decline worldwide, due to several anthropogenic stressors.
- Trace metal and metalloid pollution in the environment is an overlooked threat.
- Bees are exposed to these pollutants mainly through food and nesting resources.
- Bees suffer at the community, individual, physio-histological and microbial levels.
- Most studies used honey bees and cannot be generalised to the other 20,000 species.

GRAPHICAL ABSTRACT



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ABSTRACT

The pervasiveness of human imprint on Earth is alarming and most animal species, including bees (Hymenoptera: Apoidea: Anthophila), must cope with several stressors. Recently, exposure to trace metals and metalloids (TMM) has drawn attention and has been suggested as a threat for bee populations. In this review, we aimed at bringing together all the studies (n = 59), both in laboratories and *in natura*, that assessed the effects of TMM on bees. After a brief comment on semantics, we listed the potential routes of exposure to soluble and insoluble (i.e. nanoparticle) TMM, and the threat posed by metallophyte plants. Then, we reviewed the studies that addressed whether bees could detect and avoid TMM in their environment, as well as the ways bee detoxify these xenobiotics. Afterwards, we listed the impacts TMM have on bees at the community, individual, physiological, histological and microbial levels. We discussed around the interspecific variations among bees, as well as around the simultaneous exposure to TMM. Finally, we highlighted that bees are likely exposed to TMM in combination or with other stressors, such as pesticides and parasites. Overall, we showed that most studies focussed on the domesticated western honey bee and mainly addressed lethal effects. Because TMM are widespread in the environment and have been shown to result in detrimental consequences, evaluating their lethal and sublethal effects on bees, including non-*Apis* species, warrants further investigations.

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1. General introduction

Humanity has always been intertwined with and dependent upon the living biosphere (Díaz et al., 2018). Among the numerous “nature's contributions to people” (Chaplin-Kramer et al., 2019), pollination is undeniably a timely ecosystem service, as human demography skyrockets and reliance upon pollinated crops increases (Aizen et al., 2019; Bugin et al., 2022). Pollination is mainly provided by insects (Rader et al., 2020), including bees (Hymenoptera: Apoidea: Anthophila) (Khalifa et al., 2021), to such an extent that 19 bee and three non-bee species are currently commercially bred worldwide for pollination purposes (Osterman et al., 2021). However, scientists have sounded the alarm as wild and domesticated bee populations are vanishing (Biesmeijer et al., 2006; Koh et al., 2016; Zattara and Aizen, 2021), along with the whole entomofauna (Hallmann et al., 2017; Powney et al., 2019; Sánchez-Bayo and Wyckhuys, 2019). Some drivers of decline are widely acknowledged, such as agrochemical use, landscape management, climate change, pathogen spread and alien species introduction (Dicks et al., 2021; Wagner et al., 2021), but recently new threats have been identified as emerging (Brown et al., 2016). Among them, heavy metal pollution has gained growing attention (Singh et al., 2022; Monchanin et al., 2023; Scott et al., 2023). A search in the Scopus database showed a seven-fold increase in the number of publications about heavy metal pollution since 2000 (Fig. S1). The goal of this article is to provide a comprehensive review of the studies that assessed the effects of TMM on bees and propose a knowledge gap analysis. First, we discuss semantic issues and the misconception around TMM toxicity. Then, we focus on the routes of exposure and the role of TMM-accumulating plants. Afterwards, we examine bees' responses towards TMM exposure and the effects of TMM on bees at various biological levels, including the effects on their gut symbionts. Finally, we consider the exposure to TMM in combination or with other stressors. A Web of Science and Scopus search as well as a thorough investigation in the references of these articles yielded 59 articles around TMM pollution consequences on bees (Table S1). A graphical summary, including the major references analysed in this review, is depicted in Fig. 1.

2. Trace metals and metalloids

2.1. Moving on from semantics

From 1936 onwards, the term ‘heavy metals’ has been increasingly used in numerous areas, including the scientific literature and legislation, although an agreed-upon definition of this term is still lacking. Indeed,

controversies have come from the definitions given to ‘heavy’ but also to ‘metals’. For instance, what density should be considered to define ‘heavy’? Or should the term ‘metal’ also include metalloids? Consequently, in a ground-breaking report, Duffus (2002) ironically listed >40 definitions, bases either on density, atomic weight, atomic number and chemical or toxic properties. No consensus has been found thus far, and a handful of papers have hence suggested to abandon this term, as it is imprecise at best and misleading at worst (Chapman and Holzmann, 2007; Hübner et al., 2010; Pourret, 2018; Pourret and Bollinger, 2018; Gustin et al., 2021; Pourret et al., 2021). In this review, we opt for the term ‘trace metals and metalloids’ (hereafter ‘TMM’), as proposed by Pourret (2018) and Pourret and Bollinger (2018), that encompasses metals and metalloids (non-synthetic metals and metalloids = 76; Atkins and Jones, 1997; Silberberg and Amateis, 2021) that naturally occur at trace amounts (i.e. <1 g kg⁻¹) in the Earth's continental crust (Alloway, 2013). A screening of the Periodic Table according to this definition yields 68 elements (i.e. all metals and metalloids with the exception of Na, Mg, Al, Si, K, Ca, Ti and Fe; Fig. 2; Haynes, 2017). Trace metals and metalloid abbreviations used throughout this manuscript are those from the Periodic Table (Silberberg and Amateis, 2021).

2.2. Toxicity versus nutrition

In addition to semantic issues, another misconception around TMM concerns their toxicological properties. They have often been assumed to be hazardous and have been regarded as ‘geochemical bogey men’ (Hodson, 2004), but there has been no scientific basis to support such a generalisation (Duffus, 2002). As for every substance, TMM toxicity depends on their dose, as famously pointed out by Paracelsus (1493–1541). Actually, many TMM are essential for life (sometimes called ‘biometals’ and part of the broader umbrella term ‘micronutrients’) since they have been found to be crucial catalytic or structural cofactors in metalloenzymes as well as DNA stabilisers (Crichton, 2020). For instance, five TMM are essential to humans, namely Co, Cu, Mo, Mn and Zn (Maret, 2016), and some TMM are also essential for bees (Filipiak et al., 2021; Filipiak et al., 2022). Although we should stop considering TMM as ‘geochemical bogey men’, they display genuine toxicity when they accumulate at levels that are not tolerable by organisms, and current TMM pollution thus poses serious risks to ecosystems (He et al., 2005; Tchounwou et al., 2012; Monchanin et al., 2021a; Singh et al., 2022). Toxic concentrations of TMM are known to induce severe cellular damages, leading to carcinogenesis and neurotoxicity, mainly due to reactive oxygen species production (i.e. oxidative stress; Bower et al., 2005; Jaishankar et al., 2014).

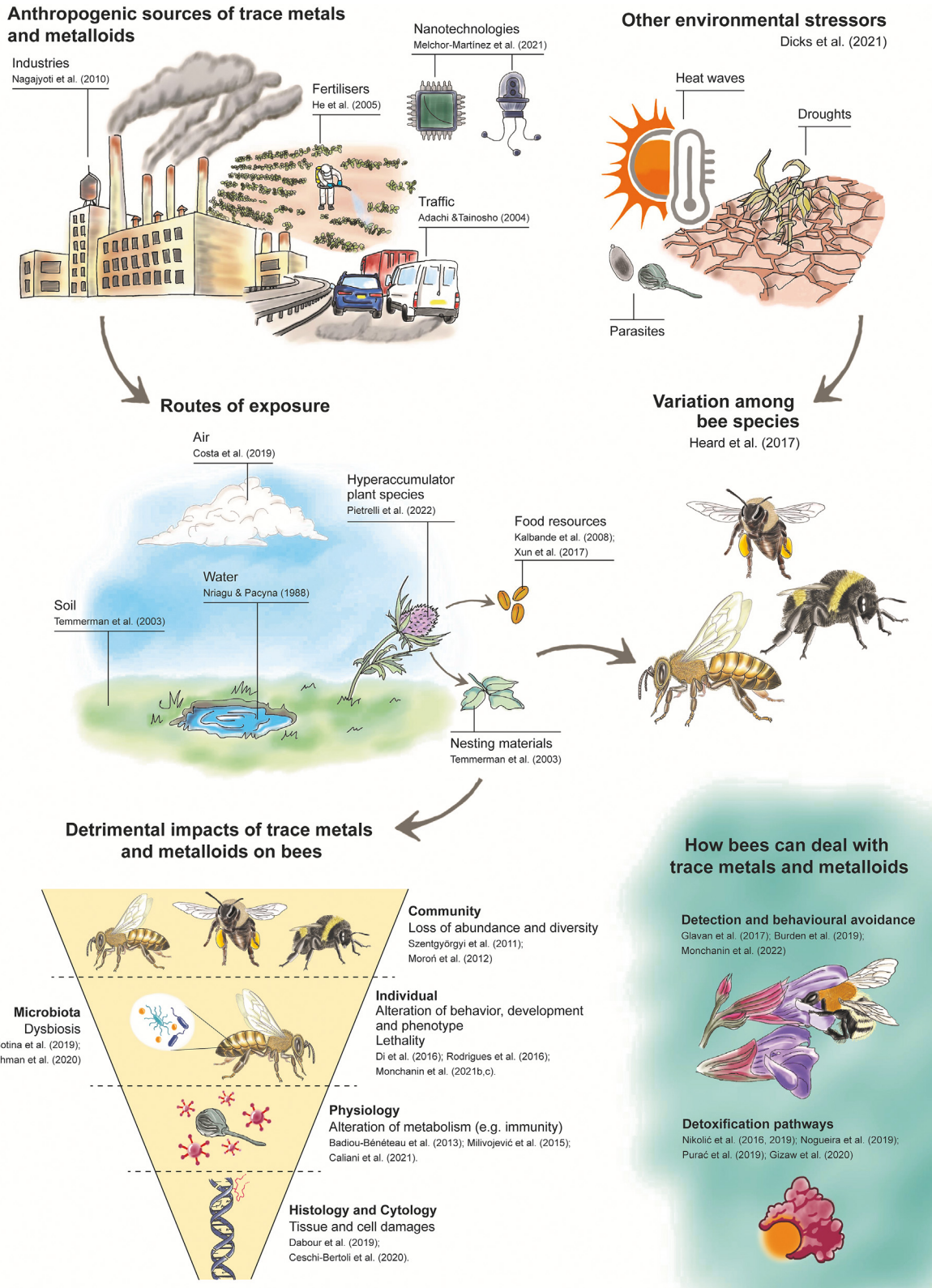


Fig. 1. Anthropogenic sources and routes of exposure of trace metals and metalloids as well as the responses and effects they trigger in bees. Major studies around the different topics are mentioned. Illustration: Maryse Vanderplank.

3. Sources and routes of exposure

Metals and metalloids naturally occur in trace amounts in soils, and their geochemical cycles are mainly driven by volcanic and degassing processes, forest fires, rock weathering, windblown dusts and sea salts.

However, hazardous concentrations of TMM may occur owing to human enterprises, such as mine tailing, smelting, agrochemical spread, animal manures, road traffic, electronic devices, sewage sludge, wastewater, coal combustion and other industrial activities (Nagajyoti et al., 2010; Wuana and Okiyeimen, 2011; Edelstein and Ben-Hur, 2018; Jayakumar et al.,

		Trace metals included in this study										Trace metalloids included in this study					Metal(loid)s found at > 1 g Kg ⁻¹ in Earth's crust	Nonmetals	Synthetic elements					
	I																	VIII						
1	H	II																	III	IV	V	VI	VII	He
2	Li	Be																	B	C	N	O	F	Ne
3	Na	Mg																	Al	Si	P	S	Cl	Ar
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr						
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe						
6	Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn						
7	Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Nh	Fl	Mc	Lv	Ts	Og						
6	Lanthanides	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu								
7	Actinides	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr								

Fig. 2. Periodic table displaying the 68 trace metals and metalloids considered in this review.

2021). For instance, TMM such as As, Cu and Pb are found in many licensed pesticides worldwide and TMM are common in fertilisers to boost crop growth (He et al., 2005). Melchor-Martínez et al. (2021) reviewed the environmental impacts of Cd, Cu, Pb and other TMM found in batteries. Defarge et al. (2018) showed that most glyphosate-based herbicides harboured harmful levels of As, Cr, Co, Ni and Pb. Also, Adachi and Tainosho (2004) found >20 TMM embedded in brake dust and tire tread, and studies repeatedly found high TMM concentrations in street dust of highly developed cities (e.g. Aguilera et al., 2021; Khodadadi et al., 2022).

Bees are exposed to TMM during their whole life through various routes, as already discussed for pesticides (e.g. Kopit and Pitts-Singer, 2018), and TMM accumulate within bee bodies as they are non-degradable xenobiotics (Raes et al., 1992; Perugini et al., 2011; Szentgyörgyi et al., 2011; Borsuk et al., 2021). TMM were found not only in pollen and nectar (e.g. Kalbande et al., 2008; Xun et al., 2017) but also in leaves (e.g. Hladun et al., 2015), water (e.g. Nriagu and Pacyna, 1988), air (e.g. Costa et al., 2019) and soils (e.g. De Temmerman et al., 2003); all these substrates represent potential routes of exposure for bees. TMM uptake can occur either internally (i.e. oral exposure) or externally (i.e. topical exposure). Indeed, all bee species are potentially exposed through food resources and water, at the larval stage while developing on food provisions, and at the adult stage while foraging and consuming resources (oral exposure). In addition to food, some bee species are likely exposed to TMM through nesting materials (topical exposure), either via leave/petal pieces or mud (i.e. cavity-nesting bees) or soils (i.e. ground-nesting bees), at the larval stage while developing on these substrates, and at the adult stage while building the nest. However, a proper demonstration of TMM exposure through nesting materials is still lacking. Finally, a transovarial route of exposure (i.e. from the mother's reproductive tract to the eggs) has been suggested for pesticides (Milchreit et al., 2016), but whether it holds for TMM remains to be investigated.

In the environment, bees are not only exposed to soluble TMM but also to TMM in fine particulate matters. The latter mostly consist of TMM oxide nanoparticles deriving from nanotechnologies (e.g. nanopesticides; Hooven et al., 2019) and industrial dusts. In industries, most TMM volatilise at high temperatures and convert to oxides which condense as fine particulate matters (Smith et al., 1995). Fine particulate matter toxicity depends on their

size (0.1–100 nm) and chemical composition (Kelly and Fussell, 2012). As for soluble TMM, intoxication may occur through ingestion but for fine particulate matters, bees may also be exposed via adsorption on the cuticle or inhalation through the tracheal system (Negri et al., 2015). The majority of the studies that exposed bees to TMM in laboratories provided TMM in aqueous solutions by using TMM salts (Fig. 3B), whereas TMM nanoparticles likely have drastic negative effects in bees given their impacts on fruit flies (e.g. El Kholy et al., 2021; El Kholy and Al Naggar, 2023). Surprisingly, there is only one study that has questioned whether a given TMM would have different effects on bees in its soluble or oxidised forms, comparing ZnCl₂ and ZnO respectively (Milivojević et al., 2015). After conductance analyses, this study showed that damages were primarily caused by soluble ions (Milivojević et al., 2015). Yet, it does not mean that poorly soluble TMM oxides are harmless for bees. On the one hand, TMM oxide nanoparticles can cross the gut epithelium and be transported into tissues, cells and even organelles (Dabour et al., 2019). On the other hand, TMM oxide nanoparticles could dissolve once present in the digestive tract, where specific physico-chemical conditions prevail (e.g. low pH), thereby increasing ion bioavailability. The way TMM oxide nanoparticles chemically behave in the bee gut is unexplored and warrants further attention. In addition, to our knowledge, no study has ever assessed the impact of TMM in fine particulate matters on bees through cuticle adsorption or inhalation.

4. Bioaccumulation in plants

TMM pollution is worrying especially as some plant species tend to accumulate TMM at high concentrations in their tissues, including floral resources (e.g. Xun et al., 2017, 2018). Basically, plants can be classified in three categories, namely metal excluders (i.e. lower concentration than in soil), indicators (i.e. similar concentration as in soil), and metallophytes (i.e. higher concentration than in soil; Dalvi and Bhalarao, 2013). Hitherto, over 450 metallophyte species have been identified (Suman et al., 2018) and there is evidence that some of them are commonly used by bees for foraging and nesting (Eskov et al., 2015; Pietrelli et al., 2022). For example, *Odontarrhena lesbiaca* was found to hyperaccumulate Ni in its floral rewards, thereby leading to Ni accumulation in several bee species (Stefanidou et al., 2020). Interestingly, this research also found that short-

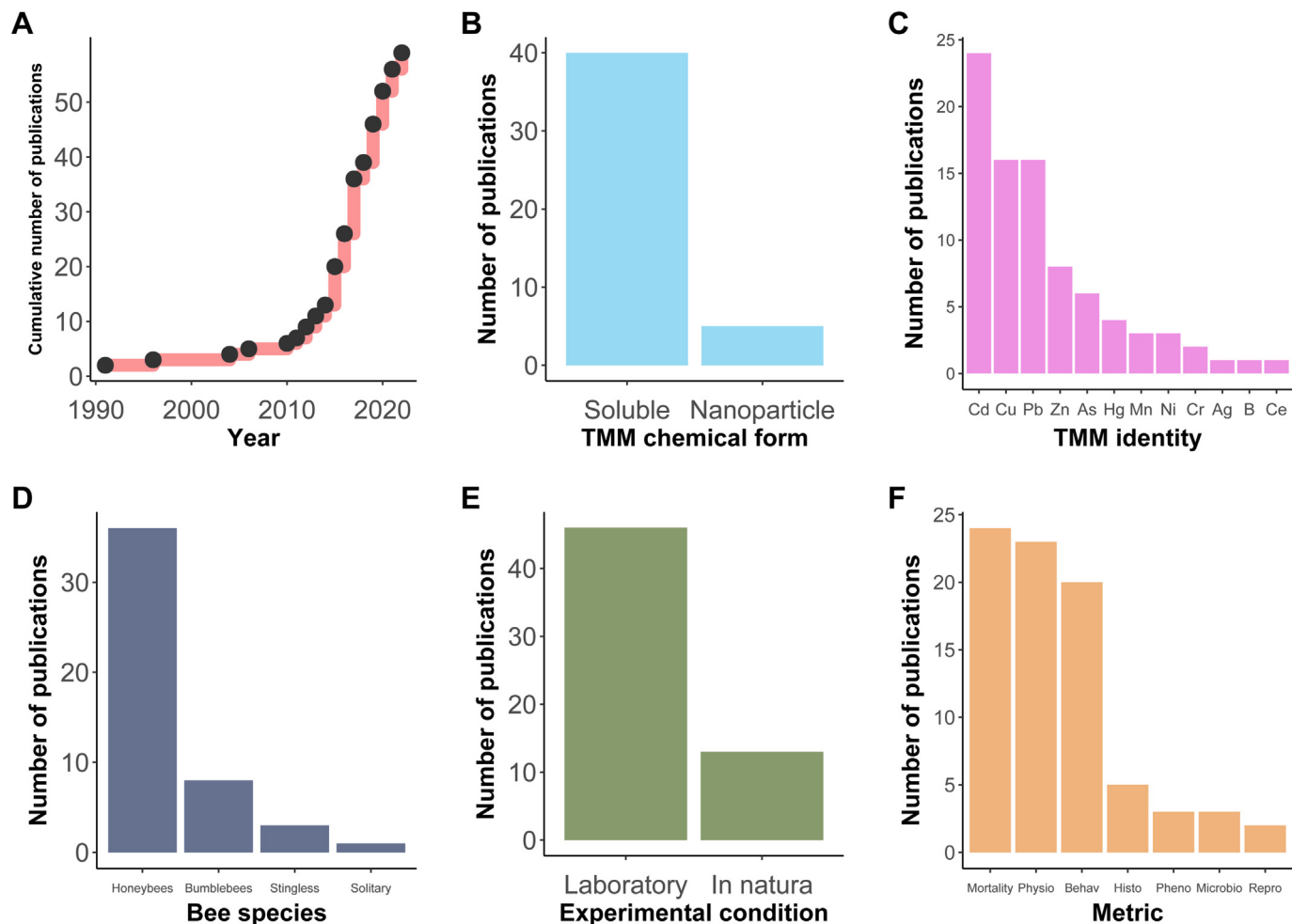


Fig. 3. Number of publications that addressed TMM impacts on bees. (A) Cumulative number of publications over time. (B) Comparison between TMM form (laboratory studies only). (C) Comparison between TMM identity (laboratory studies only). (D) Comparison between bee species (laboratory studies only). (E) Comparison between laboratory and *in natura* studies. (F) Comparison between studied metrics (laboratory studies only). All the publications are listed and detailed in Table S1.

range flying oligolectic bees accumulated higher Ni loads as *O. lesbiaca* was dominant in their foraging range and diet (Stefanatou et al., 2020). A study conducted by Meindl and Ashman (2015) found a different bee community foraging on a metallophyte species, highlighting a potential filtering mechanism through TMM accumulation. Such plants pose a threat to bees since they are increasingly used in phytoremediation strategies to chelate pollutants in TMM-contaminated soils (Salt et al., 1998; Van Aken, 2008; Ali et al., 2013), exposing bees to vast areas of TMM-rich floral resources. Stunningly, crop plants such as rapeseed and pea are used as metallophyte species in agricultural system although they are pollinated by wild and commercial bee species (Vamerali et al., 2010). Thus, caution should be paid when using bee-pollinated plants in phytoremediation schemes.

5. Bees' responses: detection, avoidance and detoxification

Bees do not forage randomly on all available resources and target specific nutrients to match their own requirements, as well as the ones of their potential nestmates and offspring (Michez et al., 2019). To assess the resource quality, bees rely on both pre- and post-ingestive cues. Pre-ingestive cues concern visual, olfactory, chemotactile and even electric information (Nicholls and Hempel de Ibarra, 2017). Bees acquired such information via numerous receptors located in sensilla found on antennae, mouthparts and other body parts (de Brito Sanchez, 2011). At the post-ingestive level, regulation could occur through physiological and histological effects (e.g. gut physical damages; Vanderplanck et al., 2020), behavioural effects (e.g. 'malaise-like' behaviour; Hurst et al., 2014; Al Naggar

et al., 2020), and potentially through brood feedback for social bee species (e.g. rate of food consumption by the larvae; Ruedenauer et al., 2016). Whether bees detect TMM in their resources at the pre-ingestive level has been recently investigated. Using proboscis extension reflex in honey bees, Burden et al. (2019) showed that Cu was rejected following antennal stimulation but was readily consumed following proboscis stimulation, while Pb was rejected only following proboscis stimulation. By contrast, Cd did not have deterrent effects following neither antennal nor proboscis stimulation (Burden et al., 2019). Monchanin et al. (2022) showed that As, Pb and Zn were rejected by honey bees when their antennae or proboscis were stimulated by solutions of these TMM. They also highlighted that when offered a choice, honey bees avoided sucrose solution spiked with Pb or Zn, suggesting reliance on post-ingestive effects. However, avoidance was only observed for high concentrations, as confirmed by electrophysiological analyses, underlying that honey bees may not be able to detect field realistic concentrations of these TMM (Monchanin et al., 2022). Even more worrying, when offered a choice, honey bees preferred solutions contaminated with ZnO nanoparticles (Glavan et al., 2017). In the wild, bees are therefore likely to collect and consume low but toxic doses of TMM.

Once ingested, the way bees excrete TMM out of their body is probably similar to the mechanism used to detoxify pesticides and phytochemicals, namely through a three-step pathway: (i) phase I functionalisation (e.g. cytochrome P450; Zhang et al., 2018; Al Naggar et al., 2020; Gizaw et al., 2020; Caliani et al., 2021; Li et al., 2022), (ii) phase II conjugation (e.g. glutathione-S-transferase; Yu et al., 2012; Badiou-Bénéteau et al., 2013; Miliivojević et al., 2015; Glavan et al., 2017; Kos et al., 2017; Nikolić

et al., 2019; Al Naggar et al., 2020; Caliani et al., 2021), and (iii) phase III excretion (Berenbaum and Johnson, 2015). In addition to this classic pathway, bees show various physiological responses to deal with TMM-induced oxidative stress and damages. It includes the increased activity/production of antioxidant enzymes (e.g. catalase; Nikolić et al., 2015; Nikolić et al., 2016; Al Naggar et al., 2020; Gizaw et al., 2020; Bernardes et al., 2021; Li et al., 2022), free radical-scavenging molecules (e.g. α -tocopherol; Gauthier et al., 2016; Nikolić et al., 2016; Jumarie et al., 2017), chaperone proteins (e.g. HSP70; Nogueira et al., 2019), and non-enzymatic metal ion-binding proteins (Badiou-Bénéteau et al., 2013; Gauthier et al., 2016; Polykretis et al., 2016; Salvaggio et al., 2017; Purać et al., 2019; Li et al., 2022). The latter, also known as metallothioneins, seem to be the flagship candidates to detoxify TMM. They harbour a low molecular weight (ca. 60 amino acids; 6–10 kDa), high cysteine content and no aromatic amino acid. The thiol groups of cysteine residues enable their binding to metal ions (Hamer, 1986; Kägi, 1991). These proteins were found to be expressed in the gut (Badiou-Bénéteau et al., 2013; Salvaggio et al., 2017), the fat bodies (Polykretis et al., 2016) and the head (Badiou-Bénéteau et al., 2013; Li et al., 2022) of TMM-treated bees. It has been proposed that TMM-bound metallothioneins are taken up by lysosomal vesicles in the midgut epithelium where TMM are retained in granules after degradation of the proteins. These granules are then expelled into the gut lumen by exocytosis or complete degeneration of the cell, before being excreted in the faeces (Dallinger, 1993). Recently, Borsuk et al. (2021) postulated that TMM are immobilised in the fat bodies and then chelated to be transported to the gut for excretion. Intriguingly, although the honey bee genome was sequenced and annotated in 2006, the first and only metallothionein gene in honey bees was identified in 2019 (Purać et al., 2019) and today, the exact way bees detoxify TMM remains uncharted. For instance, the mechanism underlying the capture and immobilisation of TMM in the fat bodies is completely unknown.

6. Effects on bees

In 2007, despite the small number of studies addressing TMM impacts on bees at that time (Fig. 3A), specialists considered TMM pollution to be one of the most important factors causing bumble bee decline in Europe (Kosior et al., 2007). Today, evidence that many TMM (Fig. 3C) impact various bee species health (Fig. 3D) is compelling, as laboratory and *in natura* studies (Fig. 3E) highlighted detrimental effects at community, individual, physiological, histological and microbial scales (Fig. 3F).

6.1. Community level: species diversity and abundance

While Szentgyörgyi et al. (2011) did not find any difference in bumble bee communities among TMM-polluted and control sites, Moroń et al. (2012) found a decreased diversity and abundance of wild solitary bees in trap nests along TMM gradients. However, the latter study did not enable to decipher whether TMM had direct (e.g. ingestion) or indirect (e.g. through the plant community) effects on these wild cavity-nesting bees (Moroń et al., 2012). We are not aware of any other study that addressed the consequence of TMM pollution on bee communities.

6.2. Individual level: mortality, reproduction, behaviour and phenotype

Trace metals and metalloids have been found to increase mortality rate (# lab studies = 24; Fig. 3F) in honey bees (Cronn, 1991; Yu et al., 2012; Özkan et al., 2014; Dağlıoğlu et al., 2015; Milivojević et al., 2015; Di et al., 2016, 2020; Hesketh et al., 2016; Hladun et al., 2016; Polykretis et al., 2016; Heard et al., 2017; Robinson et al., 2017; Sgolastra et al., 2017; Dabour et al., 2019; Al Naggar et al., 2020), bumble bees (Heard et al., 2017; Rothman et al., 2020; Scott et al., 2022), mason bees (Moroń et al., 2014; Heard et al., 2017) and stingless bees (Rodrigues et al., 2016; Botina et al., 2019), at both larval and adult stages (but see Monchanin et al., 2021b). Studies that assessed a range of doses and yielded lethal concentration 50 % (LC₅₀) are summarised in Table S2. These studies mostly

used chronic exposure designs with various durations, probably because TMM are known for their high accumulation and slow elimination, thereby making long-term exposures very relevant assessments (Hesketh et al., 2016). Research that used DEBtox predictions even showed that standard protocols (e.g. OECD, 1998) recommending 96 h acute toxicity tests could lead to overestimated tolerance levels in bees (Hesketh et al., 2016; Heard et al., 2017). For instance, there was a 27-fold difference in Cd LC₅₀ between 48 h (i.e. time used in most studies) and 720 h (i.e. worker lifespan) exposures, indicating a strong overestimation of honeybees' resistance towards Cd in the 48 h exposure design (Hesketh et al., 2016).

Besides, TMM exposure had detrimental effects on bee reproductive success (# lab studies = 2; Fig. 3F). In mason bees, Moroń et al. (2010, 2014) observed a reduced number of brood cells constructed in nests and a sex ratio biased towards females. In honey bees, Di et al. (2016, 2020) observed a longer larval developmental while Bromenshenk et al. (1991) observed fewer brood cells. In bumble bees, Sivakoff et al. (2020) and Scott et al. (2022) observed fewer larvae in the colonies. Potential differing responses between sexes and castes are unknown.

Additionally, TMM altered bee behaviour (# lab studies = 20; Fig. 3F), especially by enhancing flight take-off and vertical flight activity (Rodrigues et al., 2016), as well as by impairing walking behaviour in stingless bees (Bernardes et al., 2021). Moreover, TMM exposure modified food collection, either by increasing (Milivojević et al., 2015; Rodrigues et al., 2016) or decreasing (Hladun et al., 2016; Di et al., 2016, 2020; Al Naggar et al., 2020; Monchanin et al., 2022) food intake (but see Botina et al., 2019; Li et al., 2022). In addition, TMM were shown to impact sucrose responsiveness and learning abilities. For instance, using antennal stimulation, Mn (Ben-Shahar et al., 2004) and Pb (Burden et al., 2019) were shown to increase honey bees' ability to discriminate between sucrose solution and water, whereas Cd and Cu reduced this ability (Di et al., 2020) (but see Monchanin et al., 2021b). Later, Monchanin et al. (2021b) showed that As, Cu, Pb and their combinations impeded honey bees' short- and long-term memory abilities to discriminate between odours. Interestingly, Monchanin et al. (2021c) found that although Pb exposure did not hamper honey bees ability to discriminate two odours in a first trial, it prevented honey bees to discriminate the odours in the reverse trial, highlighting the loss of cognitive flexibility. Recently, Cd was found to alter honey bees' ability to differentiate two odours (Li et al., 2022). Finally, TMM were found to alter bee foraging behaviours. Indeed, using Ni-hyperaccumulator and non-accumulator plants, Meindl and Ashman (2015) observed a smaller visitation rate on Ni-rich plants, although bee richness did not differ. Visit duration was shortened as well, as found by Meindl and Ashman (2013) and Sivakoff and Gardiner (2017) as well as Xun et al. (2017) and Phillips et al. (2021) using bumble bees and honey bees, respectively. TMM pollution discouraged bees from visiting adjacent flowers (Meindl and Ashman, 2013) but reduced nectar robbing (Xun et al., 2018). Besides, Mn was shown to induce precocious switch from nurse to foragers and to extend foraging trip duration in honey bees (Ben-Shahar et al., 2004; Søvik et al., 2015).

Finally, TMM altered bee phenotype (# lab studies = 3; Fig. 3F). In mason bees, Moroń et al. (2014) found a decrease in larval and adult body mass while Szentgyörgyi et al. (2017) observed shorter wings but no impact on wing asymmetry with TMM pollution. In honey bees, Di et al. (2016) observed lighter pupae while Monchanin et al. (2021c) and Li et al. (2022) found a reduction in adult head size and mass.

6.3. Physiological and metabolic levels

Bees' physiological responses upon TMM exposure have been relatively well assessed (# lab studies = 23; Fig. 3F), mainly because honey bees are regarded as a sentinel species to better understand anthropogenic impacts on the environment (e.g. Badiou-Bénéteau et al., 2013). Thus, physiological biomarkers have been repeatedly examined, especially for bees' responses as described previously, to such an extent that an Integrated Biological Index has been developed (Caliani et al., 2021). Because TMM are xenobiotics impairing enzymatic activity and leading to oxidative stress that

trigger various damages (e.g. lipid peroxidation; Gauthier et al., 2016; Nikolić et al., 2016; Bernardes et al., 2021), they have been shown to disrupt several physiological mechanisms, namely (i) the production of neurotransmitters (e.g. dopamine; Søvik et al., 2015; Nisbet et al., 2018), (ii) the activity/production of synaptic enzymes (e.g. acetylcholinesterase; Badiou-Bénéteau et al., 2013; Miliivojević et al., 2015; Glavan et al., 2017; Kos et al., 2017; Nikolić et al., 2019; Al Naggar et al., 2020; Caliani et al., 2021), (iii) the production of chemoreceptors (e.g. odorant-binding proteins; Li et al., 2022), (iv) the activity/production of immune-related enzymes (e.g. lysozyme; Polykretis et al., 2016; Rothman et al., 2019; Caliani et al., 2021), (v) the activity/production of other metabolic enzymes (e.g. alkaline phosphatase; Bounias et al., 1996; Badiou-Bénéteau et al., 2013; Caliani et al., 2021; Li et al., 2022), and (vi) the respiration rate (Rodrigues et al., 2016; Botina et al., 2019).

6.4. Histological and cytological levels

Trace metals and metalloids have been shown to cause severe histological and cytological damages (# lab studies = 5; Fig. 3F), for instance to the hepato-nephrotoxic system of bumble bees, a vital system involved in haemolymph filtering and macronutrient metabolism (Abdalla and Domingues, 2015; Nogueira et al., 2019), as well as to the midgut epithelium and peritrophic matrix of honey bees (Dabour et al., 2019) and stingless bees (Bernardes et al., 2021). TMM have also been shown to reduce the number of circulating haemocytes in the haemolymph (Caliani et al., 2021). Besides, at the cytological level, Nogueira et al. (2019) and Ceschi-Bertoli et al. (2020) observed a genotoxic effect of TMM in the hepato-nephrotoxic system of bumble bees using histochemistry and a comet assay (i.e. DNA strand break quantification), respectively. Caliani et al. (2021) found increased nuclear abnormalities in haemocytes of TMM-treated honey bees. Intriguingly, Polykretis et al. (2016) observed that Cd exposure caused trophocyte and oenocyte degeneration as well as high Zn accumulation in the fat bodies of honey bees. Nogueira et al. (2019) also found such degenerated cells after TMM exposure in the hepato-nephrotoxic system of bumble bees. Dabour et al. (2019) and Bernardes et al. (2021) observed a higher proportion of autophagic and apoptotic cells in the midgut of TMM-treated honey bees and stingless bees, respectively. Overall, these studies showed that TMM impact the bee gut, hepato-nephrotoxic and fat body tissues, but whether TMM cause histological damages in other organs (e.g. brain) is unknown.

6.5. Microbial level: the importance of gut symbionts

The bee microbiota is considered as a crucial component of bee health since it positively influences bee tolerance to phytochemicals (Bonilla-Rosso and Engel, 2018), microplastics (Wang et al., 2021), pesticides (Wu et al., 2020) and parasites (Mockler et al., 2018). Conversely, such stressors can disrupt the gut symbiont community (Paris et al., 2020; Sampson et al., 2020; Al Naggar et al., 2022; Motta and Moran, 2023), leading to a dysbiosis with detrimental consequences for the bee host (Anderson and Ricigliano, 2017). TMM likely shape the host-symbiont interplay, mainly because they are cofactors of a wide range of enzymes, and are vital substrates for most microbes (Hrdina and Iatsenko, 2022). Studies addressing the tripartite bee-microbiota-TMM interaction are scarce (# lab studies = 3; Fig. 3F). In the stingless bee *Partamona helleri* Friese, Botina et al. (2019) did not observe any effect of Cu on the gut bacterial community. By contrast, Rothman et al. (2019) found a subtle disruption of the core microbiota after Cd exposure in honey bees. Interestingly, this study also showed that honey bee gut bacterial symbionts were able to remove Cd from their culture medium, hinting a potential protective mechanism for honey bees against this metal (Rothman et al., 2019). Later, after Cd and Cu exposure, Rothman et al. (2020) reported altered gut bacterial communities (including the core microbiota) in bumble bees, with a higher abundance of the opportunistic bacterium *Serratia* sp. Recently, a related study looked at the benefits of probiotic supplementation in honey bee hives to face environmental exposure to TMM. They demonstrated that

supplementation with lactic acid bacteria help honey bee workers reduce TMM accumulation within their bodies (Astolfi et al., 2022). The exact underlying mechanism remains obscure but the authors suggested that gut microbes could adsorb and absorb TMM, thereby limiting their bioavailability in the gut and facilitating their excretion (Astolfi et al., 2022).

7. Variation among bee species

Bee species vary in their routes of exposure due to their diversified nesting strategies (e.g. collection of contaminated leaves by some cavity-nesting bees; Pitts-Singer and Barbour, 2017), social organisations (e.g. queen's solitary phase; Gradish et al., 2019), foraging preferences (e.g. foraging on uncontaminated resources; Klaus et al., 2021) and morphologies (e.g. exposed surface area; Poquet et al., 2014). In addition to varying in their routes of exposure, bee species also harbour different resistance abilities towards pollutants (Sgolastra et al., 2019). In social species such as honey bees and bumble bees, pollen and nectar are mixed and stored inside specific pots for a few days before being ingested (Alford, 1975), enabling toxin dilution and detoxification by microbial exosymbionts (Ghosh et al., 2022), as well as the release of enzymes from various glands (Alaerjani et al., 2022). For instance, Borsuk et al. (2021) showed that processed honey in a hive contained eight times less Cd, eight times less Cu, and 26 times less Zn than nectar, demonstrating an efficient TMM removal during nectar processing. When feeding their larvae, social bees also attenuate toxin exposure by processing food before regurgitating it (Lucchetti et al., 2018). Besides, in social species, the colony can be regarded as a 'super-organism', with its own fitness mattering more than the fitness of its individuals. Thus, some workers dying from TMM exposure in a colony is nearly irrelevant for the colony fitness, whereas some females dying in a solitary species implies the loss of dozens of offspring individuals (Straub et al., 2015).

In addition to their social organisation, bee species further differ in their metabolism, leading to contrasting sensitivity towards pollutants. For instance, Arena and Sgolastra (2014) compared honey bee sensitivity towards pesticides with 19 other bee species. Using LC_{50} , they found that some species were 1000 times more sensitive while others were 2000 times more resistant than honey bees when exposed to pesticides (Arena and Sgolastra, 2014; but see Thompson, 2016). It is likely that bee species vary in their sensitivity towards xenobiotics because they have contrasting differences in their body sizes (Thompson, 2016). As far as TMM are concerned, Heard et al. (2017) compared As and Cd LC_{50} across three bee species (i.e. *Apis mellifera*, *Bombus terrestris* and *Osmia bicornis*). They found that after ten days, bumble bees had a lesser mortality than honey bees and mason bees when exposed to Cd while no differences were found for As. Besides, focussing on the hepato-nephrotoxic system, Nogueira et al. (2019) found that *Bombus atratus* suffered from more severe damages than *Bombus morio* after Hg exposure. To date, most studies have been conducted on the western honey bee (Fig. 3D), whereas there are >20,000 described bee species, and the western honey bee is considered as an 'outlier' in the bee world (Wood et al., 2020). Although further research is needed to compare sensitivity across bee species, it strongly suggests TMM-specific and bee species-dependant physiological capacities to cope with TMM exposure.

8. Mixtures and interactive effects

Trace metals and metalloids are rarely found alone (e.g. Lado et al., 2008) and bees are likely to encounter a combination of TMM when foraging (e.g. Hladun et al., 2015). Simultaneous exposure to several xenobiotics can lead to additive (i.e. TMM together have cumulative effects), synergistic (i.e. TMM together have a higher effect than the sum of their individual effects), or antagonist (i.e. the effect of one TMM reduces the effect of the other ones) effects, and some studies have started to investigate the consequences of such TMM multiple exposures on bees. TMM are likely to influence the distribution and impacts of other TMM since they alter the absorption and the metabolism of other compounds. In honey bees, while

Mn increases sucrose responsiveness and precocious foraging, Ben-Shahar et al. (2004) showed this effect was not observed when Zn was added to the diet. Zinc is known as an antagonist of the *malvolio* gene which enable Mn transport into brain cells, thereby explaining the antagonist effect between Mn and Zn (Ben-Shahar et al., 2004). Co-administration with Zn also reduced accumulation of other TMM in honey bee tissues (Nisbet et al., 2018; Borsuk et al., 2021), and prevented the negative effects of Cu, Cd and Pb on dopamine production, partly because Zn augments metallothionein synthesis (Nisbet et al., 2018). Robinson et al. (2017) and Dabour et al. (2019) only found additive effects between As and Cd as well as between CdO and PbO on honey bee worker mortality, respectively. By contrast, Di et al. (2020) were able to identify potential synergism or antagonism between Cd and Cu on honey bee mortality over a range of tested concentrations, using the Chou-Talalay method. Thus, they found mild synergistic effects for adult foragers but strikingly, for larvae, they found antagonist effects at low doses and strong synergistic effects at higher concentrations (Di et al., 2020). As far as cognition is concerned, As, Cu and Pb slowed down appetitive learning and reduced long-term memory specificity, but they only displayed additive effects when administered in combination (Monchanin et al., 2021b). With regards to gene expression, interactions between TMM may differ depending on the gene of interest. Indeed, feeding honey bees with CdO, PbO or their combination, Al Naggar et al. (2020) found an antagonist effect on glutathione-S-transferase expression and a synergistic effect on cytochrome P450, superoxide dismutase and catalase expressions. They also found an additive effect on acetylcholinesterase activity (Al Naggar et al., 2020). In stingless bees, Cu exposure increased food consumption and respiration rate, while a Cu-rich nutrient mix did not impact food consumption but reduced respiration rate, and none of the solutions increased mortality rate (Rodrigues et al., 2016). Recently, exposing bumble bee colonies to As, Cd, Cr, Pb or their combination, Scott et al. (2022) observed a synergistic effect on larval mortality.

9. Interaction with other stressors

9.1. Pesticides and co-formulants

In addition to being exposed to combinations of TMM, bees are also exposed to TMM together with other xenobiotics, including pesticides (Sharma et al., 2023). As for TMM, bees are exposed to pesticides through various routes, either orally or topically, both as larvae and adults, and exposure varies between bee species (Gradish et al., 2019; Sgolastra et al., 2019). In diverse living systems, simultaneous exposure to TMM and pesticides led to non-linear responses, but the way these xenobiotics influence the toxicity of one another remains unexplored (Singh et al., 2017). These interactions could either be indirect (e.g. by increasing detoxification rate; Xu et al., 2017) or direct (e.g. through molecular bonding; He et al., 2015). Research addressing the consequences of simultaneous TMM and pesticide exposure on bees is scarce, and only concerns honey bees. Jumarie et al. (2017) looked at the impact of simultaneous exposure to atrazine, glyphosate and Cd on the redox system of adult bees. They found that xenobiotics alone did not impact carotenoid level or their metabolites, which are important compounds to face oxidative stress, whereas their combination did. Using propiconazole and Cr, Sgolastra et al. (2017) surprisingly found that the binary mixture had antagonist effects only 72 h and 96 h after ingestion. Using spectrometry, they further excluded any propiconazole-Cr complex formation, suggesting that the observed interacting effect was not due to direct molecular interactions between the two xenobiotics (Sgolastra et al., 2017). Antagonist effects were also found between Cd and clothianidin (Robinson et al., 2017). It is important to stress that these few studies focussed on active ingredients, but these active ingredients do not reflect the actual effect of pesticide formulations on bees, as these formulations harbour numerous 'inert' ingredients, namely surfactants, emulsifiers and solvents (Straw et al., 2022). Assessing the interactive effects of TMM and pesticides, including their active ingredients, co-formulants and adjuvants, calls for further investigations.

9.2. Parasites and pathogens

Bees harbour a vast array of pathogens and parasites, ranging from viruses to metazoans, which play crucial roles in shaping their communities (Brown, 2022). To cope with these biotic stressors, bees display complex immune responses, at humoral and cellular levels, as well as detoxification mechanisms to prevent further damages (Evans et al., 2006; Rosales, 2017). However, exposure to TMM interferes with bees' abilities to tolerate and resist pathogens and parasites through four mechanisms (Feldhaar and Otti, 2020): (i) TMM have immunosuppressive effects (e.g. reducing lysozyme activity; Caliani et al., 2021); (ii) TMM alter detoxification mechanisms (e.g. increasing cytochrome P450 activity; Gizaw et al., 2020) which could reduce energy availability for immune responses; (iii) TMM affect bees' cognitive and motor abilities (e.g. Bernardes et al., 2021; Monchanin et al., 2021c), which could prevent them from foraging on medicinal resources (e.g. Baracchi et al., 2015); and (iv) TMM impede gut microbial symbionts, which play crucial roles in facing internal pathogens and parasites. We are only aware of one study that assessed the relationship between TMM exposure and parasite prevalence in the field. Collecting bumble bees along a TMM gradient, Szentgyörgyi et al. (2011) did not find any relation between TMM exposure and the prevalence of the microsporidium *Vairimorpha bombi* Fantham & Porter (formerly *Nosema bombi*; Microsporidia: Nosematidae). To the best of our knowledge, no study has ever focussed on the interplay between TMM and natural pathogens in bees under controlled conditions. The sole related research is Polykretis et al. (2016), which showed that honey bees injected with the gram-negative bacterium *Escherichia coli* harboured greater bacterial burden if they were treated with Cd, stressing that TMM impede bees' abilities to suppress bacterial infection.

9.3. A plethora of threats

In addition to TMM, pesticides and parasites, bees face a plethora of stressors, mainly driven by human activities, and that are likely to be found in combination. In a global-scale expert assessment, Dicks et al. (2021) pointed out that bee populations are also threatened by climate change, resource scarcity, land configuration, invasive alien species and genetically modified organisms. In a recent horizon scan, experts also highlighted potential risks stemming from nanoplastics and unchecked beekeeping (Willcox et al., submitted). These stressors are known to influence xenobiotic effects on bees. Recently, the neonicotinoid imidacloprid was shown to impair flying abilities in bumble bees but only at high temperature, hinting that extreme climate events could exacerbate xenobiotic detrimental effects on bees (Kenna et al., 2023). Additionally, nanoplastics readily adsorb pollutants due to their high surface reactivity, and could increase bee exposure to xenobiotics when they accumulate in floral resources and bee nests (Al Naggar et al., 2021). These are only two examples from uncountable combined effects among stressors. Addressing how TMM exposure may affect bees in different ways depending on concomitant stressors is urgently needed.

10. Conclusions and perspectives

The pervasiveness of human imprint on Earth is alarming, especially through the lens of biodiversity decline and extinction. In this cataclysm, bees are no exception and must cope with a myriad of stressors, most of them being increasingly studied by scientists. Quite recently, an emerging threat has drawn attention, namely the exposure to trace metals and metalloids. These elements are already ubiquitous in the environment, mainly due to human enterprises such as mining, combustion, traffic and the development of nanotechnologies. Most of bee species, regardless of their life histories and reproductive strategies, are probably exposed to these xenobiotics as larvae and adults. Research around the impacts of TMM on bees is in its infancy, but evidence has shown that TMM have detrimental consequences for wild and domesticated bees, from the community to the gut microbial levels. However, most studies have been conducted on a

domesticated species, namely the western honey bee, leaving a frightening question mark around other bee species, including bumble bees and solitary bees. Additionally, laboratory experiments have mainly focussed on lethal effects, which do not enable to fully grasp the consequences TMM may have on bee fitness. Therefore, we advocate future studies to assess the lethal effects of TMM on non-*Apis* bee species, but also the sublethal effects in control and field conditions to understand how bees respond to TMM exposure, and what the consequences for the bee offspring are. Besides, there is a need to comprehend how gut microbial symbionts shape the effects TMM trigger in bees. Because wild bees are likely exposed to several threats simultaneously, we also encourage future studies to assess the impacts of TMM alone or in combination with other stressors.

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CRediT authorship contribution statement

Antoine Gekière: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Maryse Vanderplanck:** Validation, Writing – review & editing, Visualization, Supervision. **Denis Michez:** Validation, Writing – review & editing, Visualization, Supervision.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2023.165084>.

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