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REVIEW

The implication of morphometrics and growth rate of dipteran flies in forensic entomotoxicology research: a review

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Abstract
Forensic entomotoxicology integrates toxicology into forensic entomology to estimate minimum postmortem interval (PMI_{min}) and circumstances of death where toxicants and poisonous substances are the suspected cause of death. Forensic entomotoxicology not only confirms the presence of toxicants in insects feeding off a cadaver but also studies its effect on the bio-morphometry and growth rate of insects. This review article highlights the effects of various toxicants on forensically important species of dipteran flies. It also discusses the parameters that may affect accuracy in estimation of time since death. The bio-physical effects of toxicants (excluding the analytical approach for qualitative detection) would help understand the trends in forensic entomotoxicological research worldwide.

Keywords Forensic entomology · Entomotoxicology · Postmortem interval (PMI) · Bio-morphometric · Diptera · Flies

Introduction

Forensic entomology is the application of the knowledge and study of insects to answer questions in criminal and civil cases (Catts and Goff 1992; Erzinçlioglu 2003). Various species of insects feed on the carcass, colonize it and help in its decomposition (Higley and Haskell 2009). Detritivores, mainly flies and beetles, are often associated with decomposing corpses or carcasses, body parts and other organic matters (Byrd and Castner 2010; Trees for Life 2019). The documented history and development of forensic entomology dates to the thirteenth century, and its legality in court matters dates to the late 1800s (Benecke 2001). Most of the insects of forensic relevance are from the Diptera and Coleoptera families (Goff 2009; Higley and Haskell 2009; Wells and LaMotte 2009). Insects in the dipteran family are the first to arrive and colonize a cadaver (Anderson and VanLaerhoven 1996; Grassberger and Frank 2004; Higley and Haskell 2009). Dipterans may include various flies belonging to different families, such as blowflies (Calliphoridae), flesh flies (Sarcophagidae), house flies (Muscidae) and cheese skippers (Piophilidae) (Gennard 2012). The estimation of minimum postmortem interval (PMI_{min}) or time since colonization is one of the most profound applications of this science in courts of law (Smith 1986; Erzinçlioglu 2003; Villet et al. 2009; Tomberlin et al. 2011).

Chemical substances such as drugs (including pharmaceutical preparations) and organic and inorganic poisons affect the lifecycle of insects, which is the foundation of forensic entomotoxicology (Introna et al. 2001; Campobasso et al. 2001). Forensic entomotoxicology determines the effects of toxicants on insect growth patterns, the presence of toxicants in insects feeding on a carcass and the study of bioaccumulation of toxicants, which could help investigators to determine the possible cause of death (Goff et al. 1989; Introna et al. 2001; Goff and Lord 2009). In bodies with advanced decomposition, where visceral tissues are no longer available or are not suitable for analysis, chemical extraction from insects becomes an advantageous option (Catts and Haskell 1990; Catts 1992; da Silva et al. 2017).

The main focus of entomotoxicology is the determination of chronic drug abuse or poisoning and overdose deaths (Sadler et al. 1995; Levine et al. 2000; Gosselin et al. 2011b). The field is not limited to qualitative detection of

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toxicants; it also examines how toxicants affect the size and weight changes in insects (Chophi et al. 2019). Some studies established that not only can insect larvae serve in the estimation of time since death (PMI_{min}), they are also useful for the qualitative identification of drug substances (Beyer et al. 1980; Nuorteva and Nuorteva 1982). Their growth rate and succession patterns help in the estimation of PMI_{min} (Gagliano-Candela and Aventaggiato 2001). Necrophagous flies visit the carrion during its different stages of decomposition to lay their eggs and larvae (Higley and Haskell 2009). The time since oviposition until the emergence of adult flies is known as the 'lifecycle of a fly' (Castner 2010). The lifecycle of flies varies greatly depending on temperature (Logan et al. 1976; Nassu et al. 2014), humidity (Greenberg and Kunich 2002), altitude (De Jong and Chadwick 1999; Moophayak et al. 2014), diet (Day and Wallman 2006; Rashid et al. 2008; Niederegger et al. 2013), photoperiod (Mello et al. 2012) and presence of toxicants (Introna et al. 2001; Gosselin et al. 2011b; Chophi et al. 2019). So, it is necessary to gather information about substances that affect the bionomics of various species of flies to correctly determine species and PMI (Michaud et al. 2012). Toxicants may increase or decrease the growth rate of flies (Kintz et al. 1990; Introna et al. 2001; O'Brien and Turner, 2004). PMI_{min} estimation is based solely on the extrapolation of results of studies carried out in the laboratory or field (Goff and Lord 2009; Gosselin et al. 2011b; Michaud et al. 2012).

This review primarily brings together studies to assess the toxicological effects of various drugs and poisons on flies. The effects of toxicants have been evaluated in various dipteran species as they are first to reach a carcass. In this review, the number of studies on stimulants (27%) was the highest, followed by sedatives (23%), opioids (19%), miscellaneous (17%) and insecticides (14%) (Fig. 1). The bio-physical effects of toxicants (excluding the analytical approaches for qualitative detection) and the effects of different classes of drugs or toxicants on morphometry and lifecycle have been discussed. It will enable researchers to understand the future trends of forensic entomotoxicological research findings. Studies to assess the bio-physical effects are quite scattered and variable in terms of results. Therefore, there was a critical necessity to evaluate the implications of entomotoxicology in real case scenarios by bringing them together (Pujol-Luz et al. 2008).

Insect-associated toxicology: effects of the presence of toxicants on flies

The presence of various toxicants affects the morphology as well as the lifecycle of insects (Goff and Lord 2009). It may increase the time taken until emergence or vice versa (O'Brien and Turner 2004; Tabor et al. 2005; George et al. 2009; Chophi et al. 2019). The morphology of larvae and adult insects helps in determining species and their age for the estimation of PMI (Wells and LaMotte 1995; Amendt et al. 2004; Higley and Haskell 2009; Pechal et al. 2014; Bala and Sharma 2016). The impact of multiple toxicants/chemicals on the length and weight of flies (Diptera order) is mentioned in Table 1. The lifecycle of insects plays an important role in assessing the PMI of the deceased, and morphometrics enables the estimation of the age of insects and thus PMI_{min} (Introna et al. 2001; Tracqui et al. 2004; Moffatt et al. 2016). There are several studies with the research goal of assessing the lifecycle of flies with entomotoxicology as the main approach (Table 2).

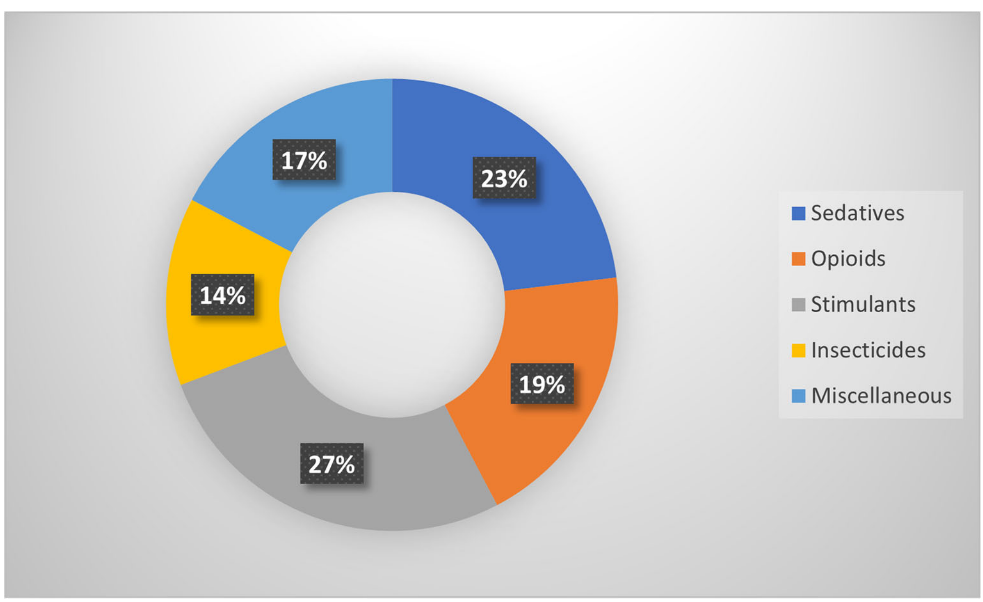

Fig. 1 Studies done on various classes of toxicants on flies ($n = 66$)

Table 1 Effect on larval length and weight of various species of flies due to various toxicants

Species	Drug/poison	Class of toxicants	Effect on insect length	Effect on insect weight	References
Chrysomya albiceps	Diazepam	Sedative	×	↑	Carvalho et al. 2001
Chrysomya putoria	Diazepam	Sedative	×	↑	Carvalho et al. 2001
Sarcophaga bullata	Amitriptyline + nortriptyline	Sedative	↓	×	Duke 2003
Calliphora vicina	Paracetamol	Analgesic	×	↑	O'Brien and Turner 2004
Calliphora vicina	Nordiazepam	Sedative	NA	NA	Pien et al. 2004
Phormia regina	Ethanol	Sedative	↑	×	Tabor et al. 2005
Lucilia sericata	Methadone	Opioid	NA	NA	Hecht et al. 2007
Lucilia sericata	Codeine phosphate	Opioid	_	NA	Kharbouche et al. 2008
Chrysomya albiceps	Codeine phosphate	Opioid	↑	↑	Fathy et al. 2008
Chrysomya albiceps	Testosterone	Stimulant	×	↑	Ferrari et al. 2008
Chrysomya megacephala	Malathion	Pesticide	NA	NA	Rashid et al. 2008
Calliphora stygia	Morphine	Opioid	NA	NA	George et al. 2009
Chrysomya megacephala	Malathion	Pesticide	↓	↓	Liu et al. 2009
Chrysomya megacephala	Buscopan®	Antispasmodic	↓	↓	Oliveira et al. 2009
Phormia regina	Oxycodone	Opioid	×	↓	Monthei 2009
Chrysomya albiceps	Nandrolone	Stimulant	×	↓	Souza et al. 2011
Chrysomya megacephala	Nandrolone	Stimulant	×	↑	Souza et al. 2011
Chrysomya putoria	Nandrolone	Stimulant	×	↑	Souza et al. 2011
Lucilia sericata	Methadone	Opioid	NA	NA	Gosselin et al. 2011a
Lucilia sericata	Tramadol HCl	Opioid	↑	×	El-Samad et al. 2011
Chrysomya megacephala	Ketum	Stimulant	↑	×	Rashid et al. 2012
Chrysomya megacephala	Ketamine	Sedative	↓	↓	Lv et al. 2012
Chrysomya rufifacies	Ketum	Stimulant	NA	NA	Rashid et al. 2013
Lucilia sericata	Ketamine	Sedative	NA	NA	Zou et al. 2013
Calliphora stygia	Methamphetamine	Stimulant	↑	↑	Mullany et al. 2014
Chrysomya albiceps	Methylphenidate	Stimulant	×	↑	Rezende et al. 2014
Chrysomya albiceps	Phenobarbital	Sedative	×	↑	Rezende et al. 2014
Chrysomya albiceps	Methylphenidate + phenobarbital	Drug cocktail	×	↑	Rezende et al. 2014
Chrysomya putoria	Methylphenidate	Stimulant	×	↑	Rezende et al. 2014
Chrysomya putoria	Phenobarbital	Sedative	×	↓	Rezende et al. 2014
Chrysomya putoria	Methylphenidate + phenobarbital	Drug cocktail	×	↓	Rezende et al. 2014
Chrysomya megacephala	Methylphenidate	Stimulant	×	↑	Rezende et al. 2014
Chrysomya megacephala	Phenobarbital	Sedative	×	↑	Rezende et al. 2014
Chrysomya megacephala	Methylphenidate + phenobarbital	Drug cocktail	×	↑	Rezende et al. 2014
Calliphora vicina	Lorazepam	Sedative	↑	↑	Altunsoy et al. 2014
Calliphora vomitoria	Nicotine	Stimulant	↓	×	Chick 2014
Calliphora vomitoria	Methamphetamine	Stimulant	↑	×	Magni et al. 2014
Chrysomya megacephala	Ketamine + xylazine	Drug cocktail	↑	↑	Singh et al. 2014
Chrysomya Putoria	Gentamicin	Antibiotic	NA	NA	Ferraz et al. 2014a, b
Chrysomya putoria	Ciprofloxacin	Antibiotic	NA	NA	Ferraz et al. 2014a, b
Calliphora vomitoria	Nicotine	Stimulant	↓	×	Magni et al. 2016
Chrysomya chloropyga	Methylphenidate	Stimulant	↑	↑	Visser 2016
Sarcophaga argyrostoma	Tramadol HCl	Opioid	↑	×	Tahoun and Abouzied 2017
Chrysomya albiceps	Tramadol HCl	Opioid	↑	↑	Ekrakene and Odo 2017
Chrysomya albiceps	Cypermethrin	Pesticide	↓	↓	Ekrakene and Odo 2017

Table 1 (continued)

Species	Drug/poison	Class of toxicants	Effect on insect length	Effect on insect weight	References
Chrysomya megacephala	Cadmium chloride	Metallic halide	↓	↓	Singh and Heer 2017
Lucilia cuprina	Anti-freeze	Ethylene glycol	↓	×	Essarras et al. 2018
Lucilia sericata	Anti-freeze	Ethylene glycol	↓	×	Essarras et al. 2018
Sarcophaga haemorrhoidalis	Chlorpromazine	Sedative	NA	NA	Nusair et al. 2017
Calliphora vomitoria	Endosulfan	Pesticide	↓	×	Magni et al. 2018
Aldrichina grahami	Methamphetamine	Stimulant	↑	↓	Wang et al. 2020
Chrysomya megacephala	Cyclophosphamide	Anti-cancer drug	NA	×	Trivia and Carvalho 2018
Chrysomya megacephala	Methotrexate	Anti-cancer drug	↓	×	Trivia and Carvalho 2018
Chrysomya albiceps	Tramadol	Opioid	↓	↓	Elshehaby et al. 2019

↑, Increased

↓, Decreased

NA, Not affected

×, Not studied

Effect of opioids

Effect on larval length and weight

Opioids remain the leading cause of accidental poisoning in the USA (Vadivelu et al. 2018). Studies have termed the opioid use disorder as an *opioid epidemic* or *the opioid crisis* because opioids (natural, synthetic and semi-synthetic) kill more people than any other kinds of drug overdose case (Gostin et al. 2017; Vadivelu et al. 2018). It affects the metamorphosis of various fly species differently (Monthei 2009). The effect of methadone and morphine on the morphometrics of *Lucilia sericata* (Hecht et al. 2007; Gosselin et al. 2011a) and *Calliphora stygia* (George et al. 2009) is not sufficient to draw any conclusive results. Oxycodone (a semi-synthetic opioid) decreased the larval weight of *Phormia regina* (Monthei 2009). Studies have reported that the presence of tramadol increased the larval length of *L. sericata* and *Sarcophaga argyrostoma* (El-Samad et al. 2011; Tahoun and Abouzied 2017). Tramadol increased the length and weight during larval stages of *C. albiceps* (Ekrakene and Odo 2017); however, another study reported that it decreased the larval weight and length of the same species (Elshehaby et al. 2019).

Effect on the growth rate of flies

Methadone and morphine did not affect the growth rate of *L. sericata* (Hecht et al. 2007; Gosselin et al. 2011a) and *C. stygia* (George et al. 2009), respectively, whereas morphine delayed the growth rate of *L. sericata* by ~24 h (Bourel et al. 1999). Codeine phosphate accelerated the growth rate of *L. sericata* (Kharbouche et al. 2008) and *Chrysomya albiceps* (Fathy et al. 2008), making their lifecycle shorter. Opioids such as oxycodone sped up the growth rate of *P. regina* during its second instar larval stage (Monthei 2009). Tramadol HCl delayed the growth rate of *L. sericata* (El-Samad et al. 2011), *S. argyrostoma* (Tahoun and Abouzied 2017) and *C. albiceps* (Ekrakene and Odo 2017).

Effect of sedatives

Effect on larval length and weight

Sedatives follow opioids as the main cause death due to overdosage (30%) in the USA (Bachhuber et al. 2016; Overdose Death Rates, USA 2018). A recent study suggests that benzodiazepines are often abused as a substitute for opioids (Sharma et al. 2018). Nordiazepam was not found to affect the morphology of *Calliphora vicina* (Pien et al. 2004). The length of *P. regina* larvae was determined to be increasing in the presence of ethanol (Tabor et al. 2005). It was ascertained that ketamine decreases the length and weight of *Chrysomya megacephala* (Lv et al. 2012), while it was not found to affect the larvae of *L. sericata* after 60 h of feeding (Zou et al. 2013). Phenobarbital increased the larval weight of *C. albiceps* and *C. megacephala* and decreased the larval weight of *Chrysomya putoria* (Rezende et al. 2014). Diazepam and lorazepam increased the larval weight of *C. albiceps*, *C. putoria* (Carvalho et al. 2001) and *C. vicina* along with their length (Altunsoy et al. 2014). Chlorpromazine was not proved to affect the morphology of *Sarcophaga haemorrhoidalis* (Nusair et al. 2017).

The cocktail of amitriptyline and nortriptyline decreased the larval length of *Sarcophaga bullata* (Duke 2003). Combination of ketamine and xylazine induced statistically significant alterations in the weight of *C. megacephala*

Table 2 Effect of various toxicants/drugs on the growth rate of forensically relevant fly species

Species	Toxicants	Rearing medium	Growth rate	References
Chrysomya albiceps	Diazepam	Rabbits	A	Carvalho et al. 2001
Chrysomya putoria	Diazepam	Rabbits	A	Carvalho et al. 2001
Sarcophaga tibialis	Sodium methohexital	Chicken liver	NA	Musvasva et al. 2001
Sarcophaga tibialis	Hydrocortisone	Chicken liver	D	Musvasva et al. 2001
Sarcophaga bullata	Amitriptyline + nortriptyline	Spiked beef tissue	NA	Duke 2003
Calliphora vicina	Paracetamol	Spiked pig liver	A	O'Brien and Turner 2004
Calliphora vicina	Nordiazepam	Spiked beef heart	NA	Pien et al. 2004
Phormia regina	Ethanol	Pigs	D	Tabor et al. 2005
Lucilia sericata	Methadone	Artificial foodstuff	NA	Hecht et al. 2007
Lucilia sericata	Codeine phosphate	Spiked pig liver	A	Kharbouche et al. 2008
Chrysomya megacephala	Malathion	Rats	D	Rashid et al. 2008
Chrysomya albiceps	Codeine phosphate	Rabbits	A	Fathy et al. 2008
Chrysomya albiceps	Testosterone	Artificial foodstuff	NA	Ferrari et al. 2008
Chrysomya megacephala	Malathion	Rabbits	D	Liu et al. 2009
Chrysomya megacephala	Buscopan®	Artificial foodstuff	D	Oliveira et al. 2009
Chrysomya megacephala	Malathion	Rabbits	D	Mahat et al. 2009
Calliphora stygia	Morphine	Artificial foodstuff	NA	George et al. 2009
Phormia regina	Oxycodone	Pig tissues	A	Monthei 2009
Phormia regina	Ethanol	Spiked pig tissues	D	Monthei 2009
Chrysomya megacephala	Malathion	Rabbits	D	Yan-Wei et al. 2010
Chrysomya megacephala	Nandrolone	Artificial foodstuff	NA	Souza et al. 2011
Chrysomya albiceps	Nandrolone	Artificial foodstuff	NA	Souza et al. 2011
Chrysomya putoria	Nandrolone	Artificial foodstuff	NA	Souza et al. 2011
Lucilia sericata	Methadone	Artificial foodstuff	NA	Gosselin et al. 2011a
Lucilia sericata	Tramadol HCl	Rabbits	D	El-Samad et al. 2011
Chrysomya megacephala	Ketum	Spiked beef tissues	D	Rashid et al. 2012
Chrysomya megacephala	Ketamine	Artificial foodstuff	D	Lv et al. 2012
Chrysomya rufifacies	Ketum	Spiked beef liver	D	Rashid et al. 2013
Lucilia sericata	Ketamine	Rabbits	A	Zou et al. 2013
Chrysomya megacephala	Paraquat	Minced beef	NA	Mahat et al. 2014
Chrysomya albiceps	Methylphenidate	Artificial foodstuff	D	Rezende et al. 2014
Chrysomya albiceps	Phenobarbital	Artificial foodstuff	D	Rezende et al. 2014
Chrysomya albiceps	Methylphenidate + phenobarbital	Artificial foodstuff	D	Rezende et al. 2014
Chrysomya putoria	Methylphenidate	Artificial foodstuff	D	Rezende et al. 2014
Chrysomya putoria	Phenobarbital	Artificial foodstuff	D	Rezende et al. 2014
Chrysomya putoria	Methylphenidate + phenobarbital	Artificial foodstuff	D	Rezende et al. 2014
Chrysomya megacephala	Methylphenidate	Artificial foodstuff	NA	Rezende et al. 2014
Chrysomya megacephala	Phenobarbital	Artificial foodstuff	NA	Rezende et al. 2014
Chrysomya megacephala	Methylphenidate + phenobarbital	Artificial foodstuff	NA	Rezende et al. 2014
Chrysomya megacephala	Ketamine + xylazine	Rats	A	Singh et al. 2014
Chrysomya putoria	Gentamicin	Artificial foodstuff	NA	Ferraz et al. 2014a, b
Chrysomya putoria	Ciprofloxacin	Artificial foodstuff	NA	Ferraz et al. 2014a, b
Calliphora vicina	Lorazepam	Spiked beef lungs	D	Altunsoy et al. 2014
Calliphora stygia	Methamphetamine	Spiked kangaroo tissues	A	Mullany et al. 2014
Calliphora vomitoria	Nicotine	Pigs	A	Chick 2014

Table 2 (continued)

Species	Toxicants	Rearing medium	Growth rate	References
Calliphora vomitoria	Methamphetamine	Spiked beef liver	A	Magni et al. 2014
Chrysomya putoria	Ampicillin	Artificial foodstuff	NA	Ferraz et al. 2016
Chrysomya megacephala	Ketamine	Rats	D	Singh et al. 2016
Chrysomya chloropyga	Methylphenidate	Spiked pig liver	A	Visser 2016
Calliphora vomitoria	Nicotine	Spiked beef liver	NA	Magni et al. 2016
Sarcophaga argyrostoma	Tramadol HCl	Rats	D	Tahoun and Abouzeid 2017
Chrysomya megacephala	Cadmium chloride	Rats	D	Singh and Heer 2017
Chrysomya albiceps	Tramadol HCl	Rabbits	D	Ekrakene and Odo 2017
Chrysomya albiceps	Cypermethrin	Rabbits	D	Ekrakene and Odo 2017
Chrysomya albiceps	Ephedrine sulphate	Dog	D	Fouda et al. 2017
Lucilia sericata	Ethylene glycol	Spiked beef liver	D	Essarras et al. 2018
Lucilia cuprina	Ethylene glycol	Spiked beef liver	D	Essarras et al. 2018
Sarcophaga haemorrhoidalis	Chlorpromazine	Spiked beef liver	NA	Nusair et al. 2017
Calliphora vomitoria	Endosulfan	Spiked beef liver	D	Magni et al. 2018
Chrysomya megacephala	Cyclophosphamide	Spiked beef mince	D	Trivia and Carvalho 2018
Chrysomya megacephala	Methotrexate	Spiked beef mince	NA	Trivia and Carvalho 2018
Chrysomya albiceps	Methamphetamine	Spiked beef liver	A	Mahmood and Kareem 2019
Chrysomya putoria	Methamphetamine	Spiked beef liver	A	Mahmood and Kareem 2019
Phormia regina	Fentanyl	Spiked beef liver	D	Robinson 2019
Lucilia sericata	Fluoxetine	Spiked pig muscles	NA	Zanetti et al. 2019
Sarcophaga crassipalpis	Fluoxetine	Spiked pig muscles	NA	Zanetti et al. 2019
Aldrichina grahami	Methamphetamine	Rabbits	D	Wang et al. 2020
Chrysomya megacephala	Lead acetate	Rat	D	Heer and Singh 2019

A, Accelerated
D, Decreased
NA, Not affected

(Singh et al. 2014). Phenobarbital, when administered along with methylphenidate, increased the larval weight of *C. albiceps* and *C. megacephala* and decreased the larval weight of *C. putoria* (Rezende et al. 2014).

Effect on the growth rate of flies

A study reported that diazepam accelerates the growth rate of *C. albiceps* and *C. putoria* (Carvalho et al. 2001), while *C. vicina* showed no effect on its lifecycle due to nordiazepam (an active metabolite of diazepam) (Pien et al. 2004). Sodium methohexital delayed the pupation of larvae of *Sarcophaga tibialis* (Musvasva et al. 2001). A combination of amitriptyline and nortriptyline did not affect the lifecycle of *Sarcophaga bullata* (Duke 2003). Research shows that ethanol delays the growth rate of *P. regina* (Tabor et al. 2005; Monthei 2009). Ketamine delayed the growth rate of *C. megacephala* (Lv et al. 2012; Singh et al. 2016) but accelerated the growth rate of *L. sericata* (Zou et al. 2013). However, ketamine, when combined with xylazine, accelerated the growth rate of *C. megacephala* irrespective of the dosage (Singh et al. 2014).

Phenobarbital alone and in association with methylphenidate increased the lifespan of *C. albiceps* and *C. putoria*, but did not affect the lifecycle of *C. megacephala* in any composition (Rezende et al. 2014). Lorazepam delayed the lifecycle of *C. vicina* (Altunsoy et al. 2014), and chlorpromazine did not affect the lifecycle of *S. haemorrhoidalis* (Nusair et al. 2017).

Effect of stimulants on flies

Effect on larval length and weight

Stimulants such as ketum (Rashid et al. 2012), methamphetamine (Mullany et al. 2014; Wang et al. 2020), nicotine (Chick 2014; Magni et al. 2016), methylphenidate (Rezende et al. 2014; Visser 2016) and anabolic steroids (Ferrari et al. 2008; Souza et al. 2011) are among the drugs whose effects on the morphometrics of certain fly species have been studied. Methylphenidate increased the larval weight in *C. albiceps*, *C. putoria* and *C. megacephala* (Rezende et al. 2014). It also increased the larval length and weight in *Chrysomya chloropyga* (Visser 2016).

Studies were also carried out on anabolic-androgenic steroids (AAS) (Ferrari et al. 2008; Souza et al. 2011). However, while AAS are sometimes classified as stimulants, their mode of action is not neural but hormonal (Rachoń et al. 2006). It does not cause a rewarding effect like other stimulants such as methamphetamine, cocaine and nicotine (Clark et al. 1996). The larval weight of *C. albiceps* increased with the increase in the dose of testosterone propionate (Ferrari et al. 2008). A similar study on the effects of nandrolone decanoate (a synthetic steroid) on three common *Chrysomya* species, viz. *C. putoria*, *C. megacephala* and *C. albiceps*, found that nandrolone decreases overall weight in *C. albiceps* larvae. On the other hand, it increases the weight of *C. putoria* and *C. megacephala* larvae (Souza et al. 2011). Studies have asserted that nicotine decreases the size of *Calliphora vomitoria* (Chick 2014; Magni et al. 2016).

Effect on the growth rate of flies

AAS such as testosterone and nandrolone, did not affect the growth rate of *Chrysomya albiceps*, *C. megacephala* and *C. putoria* (Ferrari et al. 2008; Souza et al. 2011). Methylphenidate delayed the development rate of *C. albiceps* (~24 h) and *C. putoria* (~12 h) (Rezende et al. 2014), whereas it accelerated the growth rate of *C. chloropyga* (Rezende et al. 2014; Visser 2016).

Drugs such as methamphetamine slow down the growth rate of *C. vomitoria* (Magni et al. 2014) and *Aldrichina grahami* (Wang et al. 2020), while it accelerated the growth rate of *C. stygia* (Mullany et al. 2014). The growth rate of *C. vomitoria* got accelerated in the presence of nicotine (Chick 2014; Magni et al. 2016). Ephedrine sulphate affects the lifecycle of *C. albiceps* by retarding the growth rate of the larvae (Fouda et al. 2017).

Effect of miscellaneous substances on larval development

Studies to evaluate the effects on the morphometrics of fly species due to pesticides (Mahat et al. 2012, 2014; Ekrakene and Odo 2017; Magni et al. 2018), ethylene glycol (Essarras et al. 2018), certain antibiotics (Ferraz et al. 2014a, 2014b, 2016) and prescription medicines such as paracetamol (O'Brien and Turner 2004), Buscopan® (Oliveira et al. 2009) and fluoxetine (Zanetti et al. 2019) have contributed significantly to this field. The presence of hydrocortisone (a corticosteroid) slowed the growth rate of *Chrysomya tibialis* (Musvasva et al. 2001). The most commonly available analgesic, acetaminophen (paracetamol), first seems to accelerate the growth rate of *C. vicina* from 2 to 4 days. However, it did not affect the overall lifecycle (O'Brien and Turner 2004). The results of two separate studies conducted on *C. megacephala* fed on malathion are quite dissimilar. One study reported that malathion does not affect the larval morphometry (Rashid et al. 2008), while the other reported that it decreased the morphometry (Liu et al. 2009). Another therapeutic preparation, Buscopan®, delayed the growth rate of *C. megacephala* (Oliveira et al. 2009). Gentamicin (aminoglycoside antibiotic), ciprofloxacin (quinolone antibiotic) and ampicillin did not affect the growth rate of *C. putoria* (Ferraz et al. 2014a, 2014b, 2016). Anti-cancer chemotherapeutic drugs such as cyclophosphamide delayed the growth rate of *C. megacephala* not affecting its length, while methotrexate decreased the length of the same species and did not affect the growth rate (Trivia and Carvalho 2018).

Researchers have studied the effect of pesticides to determine bioaccumulation and its effect on the growth rate of flies (Rashid et al. 2008; Yan-Wei et al. 2010; Mahat et al. 2014; Ekrakene and Odo 2017; Magni et al. 2018). Generally, pesticides are lethal to adult flies, or they act as a repellent (Rose et al. 1999). Studies have shown that malathion delayed the growth rate of *C. megacephala* (Rashid et al. 2008; Liu et al. 2009; Mahat et al. 2009; Yan-Wei et al. 2010). Malathion delayed not only the pupation but also the initial oviposition of *C. megacephala* (Rashid et al. 2008). Insecticides such as cypermethrin, α- and β-endosulfan delayed the growth rate of *C. albiceps* (Ekrakene and Odo 2017) and *C. vomitoria* (Magni et al. 2018), respectively. Herbicides such as paraquat did not affect the lifecycle of *C. megacephala* (Mahat et al. 2014). Cadmium chloride delayed the growth rate of *C. megacephala* (Singh and Heer 2017), and ethylene glycol delayed the growth rate of *Lucilia cuprina* and *L. sericata* (Essarras et al. 2018).

Discussion

Numerous studies done in the past two decades suggest developments in the field of forensic entomotoxicology (Carvalho et al. 2001; Ferrari et al. 2008; Elshehaby et al. 2019). Apart from studies on the effects of various drugs on growth rate and morphology, chemical analysis of larvae and adult stages is already in practice (Gosselin et al. 2011b; Chophi et al. 2019). The effects on the morphometry and growth rate depend on the drug/toxicants and the species of flies (Gosselin et al. 2011b; Chophi et al. 2019). It can be observed from this review that the drugs and toxicants from the same class can produce different effects even though the species of the flies may be the same. Moreover, a particular drug or toxicant can produce distinct effects on two different species.

The effects of drugs and toxicants on different fly species are such that the results cannot be generalized for the whole class of drugs. For instance, phenobarbital (a sedative)

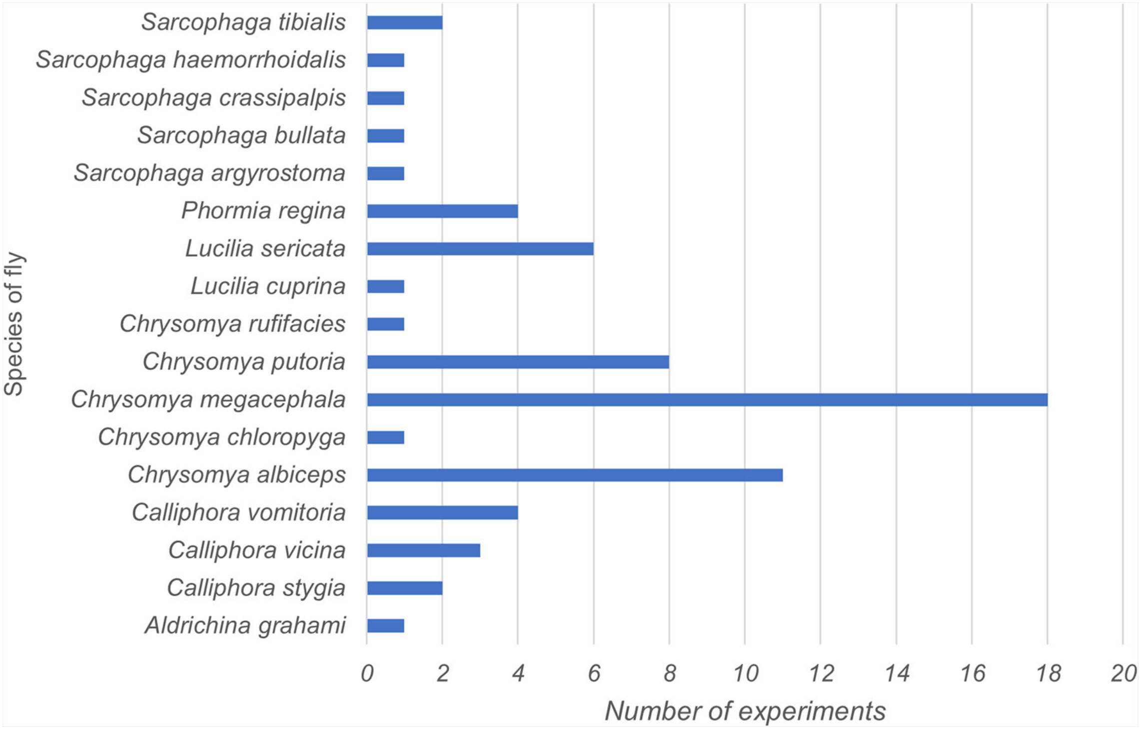

Fig. 2 Number of forensic entomotoxicological experiments on important flies to assess effects on growth rate ($n = 66$)

decreased the larval weight of *C. putoria* while it increased the larval weight of *C. albiceps* and *C. megacephala* (Rezende et al. 2014). Furthermore, phenobarbital mixed with methylphenidate (a stimulant) decreased the larval weight of *C. putoria* (Rezende et al. 2014), while methylphenidate increased the larval weight of same species when administered alone (Rezende et al. 2014; Visser 2016). Phenobarbital delayed the growth rate of *C. albiceps* and *C. putoria*, but it did not affect the growth rate of *C. megacephala* (Rezende et al. 2014). Similarly, ketamine (sedative) decreased the larval length and slowed the growth rate of *C. megacephala* (Lv et al. 2012) while the cocktail of two sedatives, i.e. ketamine and xylazine, increased the morphometrics and sped up the growth rate of same species. Such inconsistencies in results are evident from remaining studies conducted on various fly species and classes of toxicants, as mentioned in Table 1 and Table 2). Comparisons of such studies become of minimal value due to the lack of standardization of methods for conducting studies related to forensic entomotoxicology (da Silva et al. 2017). Thus, such standardization is of utmost importance and can lead to the lessening of inconsistencies in the results (Duke 2003).

The effects of toxicants on the morphometry and growth rate depend on the type of diet used as a matrix (da Silva et al. 2017). Researchers have also recommended the use of a live animal model instead of spiked tissues or artificial foodstuffs when possible (Gosselin et al. 2011b; Byrd and Peace 2012). However, while using artificial foodstuffs for rearing flies, the nutritional requirements of insects need to be taken care of (Duke 2003). The food matrix should not hinder the effects of toxicants under study (da Silva et al. 2017).

Based on the present review, it was observed that *C. megacephala* was the most studied fly species for two decades (2001–2020) and it is also the most abundant forensically relevant species worldwide (Badenhorst and Villet 2018). *C. albiceps* and *C. putoria* are the second and third mostly used dipteran species for conducting entomotoxicological experiments (Fig. 2). The abundance of these fly species makes them ideal for experiments related to forensic entomotoxicology (da Silva et al. 2017).

Present and future perspectives

Forensic entomology is progressing slowly as most law enforcement agencies are still sceptical of the potential value of this discipline (Gosselin et al. 2011b; Banerjee 2015; Sallawad et al. 2018). However, forensic entomotoxicology and entomology are lagging in medicolegal applications in some countries, such as India (Sharma and Singh 2016; Sallawad et al. 2018). Though Indian researchers have contributed significantly to forensic entomology (Kulshreshtha and Satpathy 2005; Sharma and Singh 2014; Sharma et al. 2015; Bharti 2019; Heer and Singh 2019; Dalal et al. 2020), its usage in criminal investigations is still in its infancy. A study by Dalal et al. (2017) states that many study parameters are possible and there is a critical necessity to include entomological evidence in routine casework. The authors are optimistic that this field has much more to contribute to forensics. There is a need to carry out more studies, as the statistically relevant constants and variables (in terms of species, environment, nutrients, toxicants, metabolites, tissue types/matrix and sample size) can draw more conclusive results in future work to easily extrapolate the findings to casework.

While the collection of entomological evidence for toxicological analysis in forensic laboratories is still a matter of debate, especially in the middle to lower middle-income countries (Tomberlin and Benbow 2015), it has improved the way death investigation takes place (Sharma and Singh 2016). Unfortunately, forensic labs in India are not equipped to examine entomological evidence (Singh et al. 1999; Banerjee 2015), but the way the discipline is growing in terms of relevant research an encouraging future is in sight. The number of research studies in forensic entomotoxicology suggests that it will become a routine in investigation of crimes by the law enforcement agencies (Sharma and Singh 2016).

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