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A dynamic energy budget (DEB) model to assess the sublethal effects of imidacloprid toward *Gammarus pulex* at different temperatures

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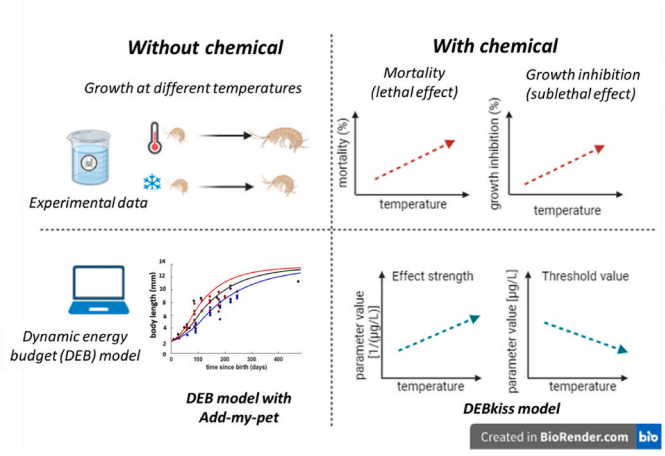
HIGHLIGHTS

- The experimental setup of *G. pulex* demonstrated consistency and reproducibility.
- *G. pulex* exhibits accelerated growth at higher temperatures.
- Environmental concentrations of imidacloprid have limited effects on *G. pulex*.
- The DEB model revealed that organism thresholds are lower at higher temperatures.

GRAPHICAL ABSTRACT



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ABSTRACT

Environmental ambient temperature significantly impacts the metabolic activities of aquatic ectotherm organisms and influences the fate of various chemicals. Although numerous studies have shown that the acute lethal toxicity of most chemicals increases with increasing temperature, the impact of temperature on chronic effects — encompassing both lethal and sublethal endpoints — has received limited attention. Furthermore, the mechanisms linking temperature and toxicity, potentially unveiled by toxicokinetic-toxicodynamic models (TKTD), remains inadequately explored. This study investigated the effects of environmentally relevant concentrations of the insecticide imidacloprid (IMI) on the growth and survival of the freshwater amphipod *Gammarus pulex* at two different temperatures. Our experimental design was tailored to fit a TKTD model, specifically the Dynamic Energy Budget (DEB) model. We conducted experiments spanning three and six months, utilizing small *G. pulex* juveniles. We observed effects endpoints at least five times, employing both destructive and non-destructive methods, crucial for accurate model fittings. Our findings reveal that IMI at environmental concentrations (up to 0.3 µg/L) affects the growth and survival of *G. pulex*, albeit with limited effects, showing a 10% inhibition

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compared to the control group. These limited effects, observed in both lethal and sublethal aspects, suggest a different mode of action at low, environmentally-relevant concentrations in long-term exposure (3 months), in contrast to previous studies which applied higher concentrations and found that sublethal effects occurred at significantly lower levels than lethal effects in an acute test setting (4 days). Moreover, after parameterizing the DEB model for various temperatures, we identified a lower threshold for both lethal and sublethal effects at higher temperatures, indicating increased intrinsic sensitivity. Overall, this study contributes to future risk assessments considering temperature as a crucial factor and exemplifies the integration of the DEB model into experimental design for comprehensive toxicity evaluations.

1. Introduction

Recently, there has been growing interest in integrating natural stressors like temperature into conventional toxicity tests to better understand the future impact of global warming (Wiles et al., 2020; Macaulay et al., 2021). Temperature is a critical factor in biological processes, particularly for aquatic ectothermic species, where it can affect growth, feeding, and reproduction, usually, high temperature speeds up these processes but could also result in thermal stress towards ectothermic species (Burraco et al., 2020). Additionally, temperature can influence the behaviour of chemicals in the environment, including their fate and bioavailability (Harwood et al., 2009; Camp and Buchwalter, 2016). While several studies have investigated and revealed that higher temperatures can enhance the acute lethal toxicity of pollutants (Camp and Buchwalter, 2016; Macaulay et al., 2020), relatively little is known about the impact of temperature on longer-term chemical exposure scenarios on both lethal and sublethal effects.

Moreover, for comprehending the mechanisms underlying the combined impact of temperature and chemicals at both lethal and sublethal levels, the framework available is the Dynamics Energy Budget (DEB) model. The theory of DEB provides a general framework for the metabolic organization and specifies the rules for the acquisition and use of energy of individual animal organisms over their entire life cycle, i.e., how organisms acquire and use resources for growth, development and reproduction (Baas et al., 2010; Jager et al., 2015). DEB models can apply DEB theory to (eco)toxicological issues, functioning as a toxicokinetic-toxicodynamic (TKTD) approach for sublethal effects combined. The model analyses sublethal endpoints (commonly growth and/or reproduction) from temporally resolved toxicity experiments and utilises energy budgets of the corresponding organism to predict sublethal effects of untested conditions (EFSA PPR et al., 2018). Effects on survival are strictly speaking not DEB related but can be easily incorporated into the framework.

The DEB model describes these life-cycle processes with several species-specific parameters, such as ultimate total length, growth efficiency, etc. These parameter values are gathered in the Add-my-pet database, which is freely accessible and contains the physical characteristics of more than 4000 species (http://www.bio.vu.nl/thb/deb/deblab/add_my_pet/index.html). When employed in conjunction with stressors, DEB models can identify the change in energy allocation due to a stressor and determine its physiological mode of action and the extent of this change. The five commonly used physiological modes of action in ecotoxicology are a decrease in assimilation, an increase in the costs for maintenance, growth or reproduction, and a direct hazard to the embryo (Jager and Zimmer, 2012; Ashauer and Jager, 2018). In simple terms, up to a threshold level, damage caused by a stressor can be tolerated by the organism without any negative impact. However, beyond this threshold, damage leads to a linear increase in survival hazard or physiological stress, resulting in sublethal effects. To describe this damage process, a series of parameters are used, including dominant rate constants, effect thresholds, and effect strength. For a more comprehensive understanding of DEB models, additional literature should be consulted (Van der Meer, 2006; Jager, 2016; Sherborne and Galic, 2020; Jager et al., 2023).

Numerous ecotoxicological studies have predominantly centred on laboratory-raised species, including *Daphnia magna* (Serra et al., 2020; Im et al., 2022) while investigations involving field-collected species remain scarce. In this study, we explore the feasibility of using a field-collected species, *Gammarus pulex*, an invertebrate species that is common in streams and ditches of Northern Europe, to investigate the influence of temperature on the toxicity of pesticides. *G. pulex* is an important ecological bioindicator that plays a vital role in the degradation of leaf litter in aquatic systems (Dangles et al., 2004). The lifespan *of G. pulex* varies between 1 and 2 years (Sutcliffe et al., 1981). These organisms reach maturity at approximately 6 mm in body length (equals approximately 3 months), with maximum adult sizes averaging around 12 mm for females and up to 16 mm for males. Additionally, their growth rate is notably affected by changes in temperature (Welton, 1979; Welton and Clarke, 1980). Previous studies have found that *G. pulex* is sensitive to both temperature and pesticides, including IMI (Mangold-Doring et al., 2022; Huang et al., 2023), a widely used insecticide that inhibits the feeding rate of *G. pulex* and affects the nervous system (Agatz et al., 2014). In addition, for *G. pulex*, its mortality rate increases rapidly above its optimal temperature of 18 °C, making it a good candidate for investigating the combined effects of temperature and pollutants (McCahon and Pascoe, 1988; Foucreau et al., 2014).

Our study aims to determine how temperature affects the lethal and sublethal impacts of IMI on *G. pulex*, using a DEB model. We examine these effects at environmental IMI concentrations (0, 0.01, 0.1, 0.3 μg/L) over 3 and 6 months at 11 °C, reflecting natural conditions in the Netherlands, and 15 °C, anticipating warmer climates. These environmental concentrations were chosen to cause sublethal and moderately lethal effects in the long-term experiment, as we aimed to measure the organism's growth without causing high mortality. Ultimately, our study seeks to address a significant knowledge gap regarding how temperature interacts with chronic low levels of chemical exposure in aquatic organisms. It offers crucial insights into the ecological impacts of pesticides in the context of climate change and showcases the practical application of DEB models in ecotoxicological research.

2. Materials and methods

The experimental and modelling efforts focus on the effects of temperature and IMI on mortality and growth inhibition. We applied the standard DEB model to *G. pulex* under the exposure of IMI combined with different temperatures to approach our research goals.

2.1. Experimental setup

The experimental data used for model calibration in this study were obtained from dedicated experiments in the present study and a study that has already been published (Huang et al., 2023) (Table 1). The 90-day experiment (Expt B) which started in April 2021 and a 180-day (Expt A) experiment starting in April 2022. For ease of reporting the results and understanding the experiments will not be reported in chronological order (SI).

2.1.1. Choice of chemical and test organism

Imidacloprid (IMI) is a widely used insecticide that is frequently

detected in the aquatic environment due to its extensive usage and specific chemical properties, such as high water solubility, low volatility, and high DT_{50} values in water and soils (Bayer, 2012; Nauen et al., 2015; Lewis et al., 2016; Pietrzak et al., 2020). Despite being banned in the EU since 2018, measured environmental concentrations of IMI still range from 2.7 ng/L to approximately 10 μg/L (Hladik et al., 2018; Pietrzak et al., 2019; Barbieri et al., 2021; Casillas et al., 2022). The predicted No-Effect Concentration (PNEC) for IMI has been reported as 0.009 μg/L (Carvalho et al., 2016) in the stream for various species. In this study, IMI concentrations of 0.01, 0.1, and 0.3 μg/L were chosen to represent the common environmental concentration range of IMI in Europe (Pietrzak et al., 2019). These concentrations were intended to cause sublethal effects and moderately lethal effects in the long-term experiment since a previous study found that the LC_{10} of IMI was 0.1 (0.02–3.0) μg/L after 28 days of exposure at 15 °C (Huang et al., 2023).

Imidacloprid (IMI; CAS: 138261-41-3, purity ≥98%) was obtained from Sigma Aldrich, and the stock solution of IMI was dissolved in Milli-Q water. *G. pulex* was collected from an uncontaminated brook, the Heelsumse brook near Wageningen, The Netherlands (coordinates 51.973400, 5.748697) in March 2021 for the first growth experiment and March 2022 for the second growth experiment. This brook is groundwater-fed and cool in summer. The brook's yearly water temperature range is from 4 °C to 17 °C based on personal observation. The culture conditions for the organisms in this study were similar to those described in previous studies (Huang et al., 2023). More specifically, for 90-days experiment, after field collection, healthy juvenile individuals (without parasites seen as an orange dot on the back) with similar length (around 4 mm) were randomly selected and put into three buckets with a mixture of field water and pre-aerated groundwater from the Sinderhoeve experimental station (the Netherlands; www.sinderhoeve.org). In the laboratory, *G. pulex* was acclimatized in two water bath sections at field temperature (11 °C) for two days. Subsequently, the temperature in 15 °C culture was gradually increased the experimental temperatures at a rate of 0.5 °C per hour, while the temperature in the 11 °C culture remained unchanged. The intended temperatures were 11 ± 1 °C and 15 ± 1 °C. After each section reached its experimental temperature, *G. pulex* was acclimatized for at least another two days before exposure. During the acclimation period, organisms were fed leached *Populus* leaves ad libitum. A light-dark regime of 12:12 h was used.

For the 180-day experiment, we collected larger adult organisms (about 10 mm). They underwent the same temperature setting procedures as in the 90-day experiment. These organisms were cultured in the lab for approximately 1 month at different temperatures to produce enough offspring for our experiment.

During the acclimation or culturing period, the organisms were fed leached Populus leaves ad libitum. A light-dark regime of 12:12 h was maintained. Additionally, the offspring were fed with the fecal slurry of adults.

2.1.2. Experimental design

Two long-term growth experiments were conducted, and one individual juvenile *G. pulex* (2–4 mm) was utilized in each test system to investigate the allocation of energy towards assimilation, maintenance, and growth processes. The experiments were conducted in 100 mL glass jars with 100 mL of groundwater. Experiment A had five replicates at each time point for each concentration and each temperature, while Experiment B had twenty replicates for the control group and fifteen replicates for the chemical treatment groups. Reproduction was not examined in the current study. After climatization in a water bath (2.1.1), the experiments were conducted in two separate climate rooms with temperature monitored, and the measured temperature was within the 1 °C deviation of the intended temperatures.

2.1.2.1. Experimental A (180 days). In this 180-day experiment, single *G. pulex* (2 mm) obtained from lab-raised females were added to 100 mL jars containing 0, 0.01, 0.1, or 0.3 μg/L of IMI, with a special diet of adult stool slurry for small juveniles. The experiment was initiated with *G. pulex* 30 days old at 15 °C and 60 days old at 11 °C. The variation in ages was attributed to logistical considerations in managing the workload. When the organisms reached the size of 5 mm, conditioned Populus leaf (Ø 17 mm) was added as food. Monthly, animals were carefully transferred to newly spiked systems, which contained a layer of gravel, a piece of metal mesh, and conditioned leaf or adult stool slurry. At each renewal, five replicates for each concentration were destructively sampled randomly and the animals were preserved in the freezer for further length measurement. Initially, there were 30 replicates each containing one individual for each treatment, and after each month, 5 replicates were sampled destructively, allowing us to measure the length, head width and dry weight of the individuals, see below section 2.1.4 There were a total of 240 test systems initially with four concentration levels per temperature, with systems reduced over time through destructive sampling.

2.1.2.2. Experimental B (90 days). In the 90-day experiment, juvenile *G. pulex* (4 mm), collected from the field, were added individually to 100 mL jars after lab and temperature acclimation, as described above. Each jar contained concentrations of 0.01, 0.1, or 0.3 μg/L of IMI and was supplied with a conditioned Populus leaf (*Ø* 17 mm) as food. In addition, the jars contained a layer of gravel, and a piece of metal mesh to provide optimum living conditions for *G. pulex*. The experiment was performed at two temperatures: 11 °C and 15 °C. Monthly, the animals were carefully transferred to the new jars with fresh solutions. During the renewal, the size of all living animals was measured before they were transferred to the new system. There were 20 replicates for the control group and 15 replicates for other treatment groups, every month, all replicates were checked non-destructively and measured.

2.1.2.3. Experiment C (Effects on survival of 28 days experiment from the literature). The 28-day toxicity data at 7, 11, and 15 °C originates from a previous study (Huang et al., 2023). Briefly, during this 28 day experiment, 11 juvenile *G. pulex* (4.2 ± 0.7 mm) were exposed to 1 L of water at concentrations of 0, 0.3, 1, 3, 10 or 30 μg/L of IMI. Two pieces of

Table 1
Summary of experimental data and model application.

Experiment name	Exposure concentration (μg/L)	Initial size (mm)	Initial age of animals	Temperature	Experimental durations	Applied model	Purpose	Data source
A: Growth experiment of control groups	Control	2	30 days old at 15 °C, 60 days old at 11 °C	11 °C, 15 °C	180 days	physiological *G. pulex* DEB model	Validate the reproducibility of the available model	This study
B: Effects of IMI on sub-lethal endpoints	Control, 0.01, 0.1 and 0.3	4	Unknown	11 °C, 15 °C	90 days	DEBkiss-tox model	Assess the effects of imidacloprid	This study
C: Effects on survival from the literature	Control, 0.3 1, 3, 10, and 30	4	Unknown	11 °C, 15 °C	28 days	GUTS-SD	Validate the GUTS model with long-term (90 days) data	Huang et al. (2023)

conditioned Populus leave (Ø 32 mm) and aeration were provided. The mortality of the organisms was measured every two or three days. There were 5 replicates for the control group and 3 replicates for treatment groups. The biggest difference between the study by Huang et al. (2023) and the present study was the number of individuals in each replicate, 11 in the Huang et al. (2023) study, and 1 in the present study.

2.1.3. Chemical analysis

Clean surface water has been analysed by LC/MS-MS to confirm the IMI concentrations, and no background contamination has been detected. The light in the experiments did not contain ultraviolet light to prevent the photodegradation of IMI which was confirmed by the analytical measurement with LC/MS-MS. Every month, two random samples of each concentration level from old and new jars were taken to verify the concentrations. All water samples were analysed by reversed-phase liquid chromatography-tandem mass spectrometry (LC-MS/MS) based on the measurement of IMI as described by (Huang et al., 2023). The analyses were performed on an Agilent 1260 Infinity liquid chromatography coupled with a 6460 Triple quad mass spectrometer (Agilent Technologies, USA). The limit of quantification (LOQ) of IMI in water samples was 0.01 μg L^{-1} and the limit of detection (LOD) was 0.003 μg L^{-1} (Support information).

2.1.4. Sublethal endpoints assessment

During the Expt A, measurements required destructive sampling, which involved taking five replicates from each treatment every month. The sizes were measured after freeze-killing. In the meantime, the head width and dry weight of the individuals were also determined. During the Expt B, size measurements were performed non-destructively and all alive animals were sized monthly, handled gently, and returned to the renewed systems. Systems containing a dead individual were discarded. Besides the size, at the end of the 90-day experiment, we identified the sex of the remaining organisms. For more details about these endpoints, please see the SI.

Quality requirements were met for all experimental data: (1) mortality in the control group was lower than 20%; (2) The measured water concentrations consistently fell within the range of 80%–120% of the nominal concentration, demonstrating stability with a maximum deviation of 20% over the course of a month; (3) The monthly measured water parameters, including temperature, pH, oxygen, and conductivity, remained relatively stable with a maximum deviation of 20% over the course of a month; (4) no parasites were observed in any of the living *G. pulex* during the experiments.

2.2. DEB model calibration and GUTS model validation

We used the BYOM MATLAB package (available at debtox.info/byom.html) to fit the model parameters to the experimental data (Table 1). The optimisation of the parameter values was performed with the parameter space explorer. This algorithm combines grid search, a genetic algorithm, and likelihood profiling, giving the Confidence Intervals (CIs) of the parameter values. For all models, the fitting efficiency (R^2) and Normalized Root Mean Square Error (NRMSE) were used in our study to evaluate model performance (EFSA PPR et al., 2018).

Note that we employ the full DEB model in combination with *Add-my-Pet (AmP)* for analyzing growth data in control groups (Section 2.2.1). The full set of physiological parameters, see Table S1. However, for chemical effects, we use the DEBKiss-tox model (Section 2.2.2), which allows for simplified model fitting. More details are provided below.

2.2.1. DEB growth model calibration

In the Expt A, the age of the tested animals was known, thus, we can track the growth, and apply 'add-my-pet' parameters to it. We evaluated the performance of an existing complete model, the physiological *G. pulex* model (*stdDEB-TKTD_v11, byom_stddeb_Gammarus.m*), by running it with our experimental data at various temperatures without any modification.

This physiological DEB model accounts for temperature influences by applying a temperature correction with an Arrhenius relationship to the assimilation and maintenance processes, keeping the values of each parameter constant (Teal et al., 2012). But, using our data at each temperature, we could assess the potential effect of temperature on each specific parameter, such as partition fraction, and scaling food density (Table S1). Therefore, for each temperature, we tuned each parameter separately to explore whether the parameter shows temperature dependence and evaluate if we can get a better fit with temperature correction (Table S1). The smallest Akaike Information Criterion (*AIC*) value was used to select the best model.

2.2.2. DEBkiss-tox model calibration

To fit the toxic effects of IMI at different temperatures, a DEBkiss-tox model was applied. DEBkiss is a simplified DEB model framework for animals that completely removes the reserve compartment; given the continuous feeding provided during this experiment, concerns related to the reserve compartment can be disregarded (Jager, 2016; Sherborne et al., 2020). Our DEB-tox model was modified based on DEBtox2019 (Version 4.5b, 2022) from the BYOM platform (https://www.debtox.info/debtoxm.html). In this model, we used simplified 'add-my-pet' parameters for all temperatures, with Lm (maximum length) set at 13.8 mm and Lb (length at puberty) set at 6.6 mm. Firstly, the control data of this study were fitted to estimate the growth rate (*rB*) of *G. pulex*. Then, the treatment data were fitted to estimate the parameters of *kd* (dominate rate constant), *zb* (the threshold for sublethal effects) and *bb* (effect strength for sublethal effects), *zs* (the threshold for lethal effect) and *bs* (effect strength for lethal effect). Next, we selected the mode of action (a decrease in assimilation, an increase in the costs for maintenance or growth) with the smallest Akaike information criterion (*AIC*) value as the best model. There were no significant differences when *AIC* value differences were less than 3. The mode of action regarding reproductions was not investigated in this study, as this was not assessed in the experiments.

In addition, we used a putative non-toxic concentration as the lower limit of the effect threshold in the model fits. This putative non-toxic concentration of 0.01 μg/L was derived from our experiment which was also the lowest concentration we used and had no significant effects compared to the control group. Putative threshold values provide prior information resulting in a more realistic and better model fits (finite confidence interval) (Delignette-Muller et al., 2017).

Furthermore, to compare the consistency of our two experiments, we compared the control growth from different experiments (180-day and 90-day experiments). We also explored the potential growth difference between sexes in the control groups of the 90-day experiment.

2.2.3. GUTS model validation for survival

In the past decade, the development of the General Unified Threshold model for Survival (GUTS) framework firmly established the concept of damage dynamics, which takes place between internal concentration and survival (Jager et al. 2023). Also, GUTS models can be used to predict survival under other independent exposure conditions (EFSA PPR et al., 2018).

To validate the effects observed in the 90 days current study we used data from a shorter-term experiment, i.e. the 28 days experiment by Huang et al. (2023). For modelling, we used a standalone software, *OpenGUTS*, to calibrate the GUTS model parameters and make the validation on the lethal data of our present study (https://openguts.info). The 28d-study evaluated the toxicity of IMI to *G. pulex* at different temperatures (7, 11, and 15 °C) for 28 days. This study assessed the mortality of *G. pulex* at a range of IMI concentrations (0–30 μg/L) at different time points. The published data was used to calibrate the model and the calibrated model was used to validate the survival of *G. pulex* in

the present study. It is worth noting that in the prediction analysis, only stochastic death (SD) was considered since the DEB model solely incorporates stochastic death mechanisms. For more details about the calibration and validation, please see the SI.

2.3. Data analysis

The significant differences in sublethal endpoints, e.g., the size among treatments at each temperature and each time point, and the dry weight of animals at each temperature at the end of the experiment, were assessed. The assumptions of normality were evaluated using a Shapiro-Wilk test, and the assumption of equal variance was evaluated using a Spearman rank correlation between the residuals and the dependent variable. If the assumptions of normality and equal variance were passed, a one-way analysis of variance (ANOVA) with $\alpha = 0.05$ and a post-hoc *Tukey's test* was conducted. If assumptions failed, a *Kruskal-Wallis* test, with $\alpha = 0.05$, and a post-hoc Dunn's test were used. A two-tailed p-value ($p < 0.05$) was considered to be statistically significant. A Bonferroni correction approach was adopted when multiple comparisons were made.

3. Results

3.1. The growth of Gammarus pulex in the control groups (without chemical application) at different temperatures

3.1.1. Experiment A: the growth of G. pulex in 180-day experiment

In Expt A, the control treatment showed less than 20% mortality at each time point. The organisms in the control group at 15 °C grew from 2.4 to 9.5 (±0.5) mm after 170 days (Fig. 1), and the growth rate was 0.0058 (0.0051–0.0064) d^{-1} (Fig. 2). while the organisms in the 11 °C control group grew from 2.9 to 9.1 (±0.3) mm after 186 days (Fig. 1), and growth rate was 0.0045 (0.0041–0.0048) d^{-1} (Fig. 2). Based on our experimental results, we found that the growth rate increased with higher temperatures (Fig. 2).

In terms of model fitting, we utilized the established physiological *G. pulex* DEB model *(stdDEB-TKTD_v11, byom_stddeb_Gammarus.m)* originally derived from a growth study conducted at 13 °C (McCahon and Pascoe, 1988). We applied our experimental control data to this existing *G. pulex* physiological model and plotted the model's predictions alongside our data (Fig. 1). This plot demonstrates a relative alignment between the model's predictions and our experimental data, affirming the model's suitability for extrapolation to two untested temperature conditions.

Furthermore, to explore the impact of temperature, we

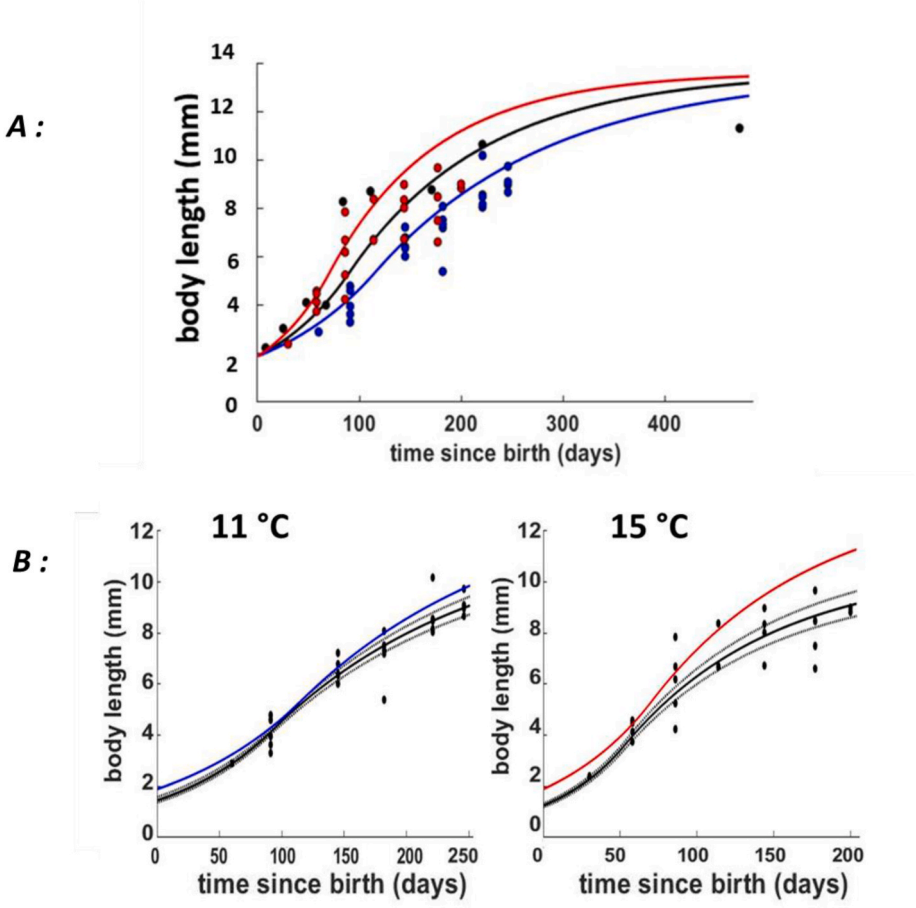

Fig. 1. A: The growth of *G. pulex* in the control group at different temperatures over a Expt A (180 days). The lines represent the model fit using default parameters from byom_stddeb_Gammarus.m without modifications. The blue line indicates predicted growth at 11 °C, and the red line at 15 °C. The black line represents 13 °C data sourced from Mccahon and Pascoe (1988) (n = 1). Blue and red dots represent experimental data from the current study. B: The growth of *G. pulex* at 11 °C (left) and 15 °C (right). Black dots, lines, and dashed lines depict experimental results, the fitted curve, and the confidence interval, respectively, after modifying the kappa parameter in the DEB model. The blue line and red line represent model fittings without any adjustments. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

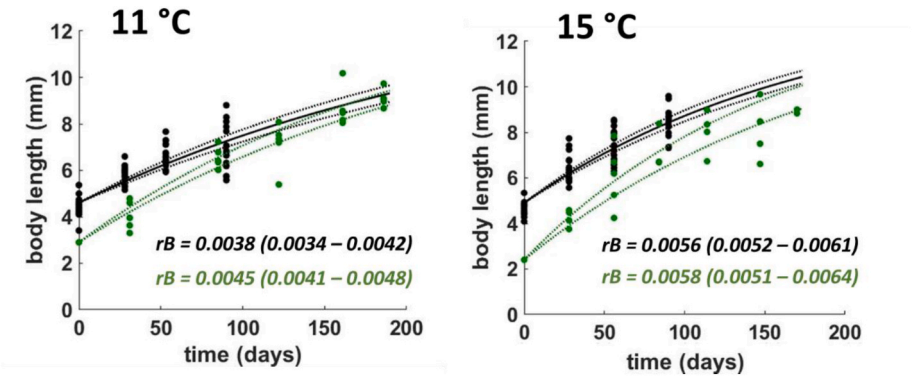

Fig. 2. The growth of Gammarus pulex in the two growth experiments. The results at 11 °C (left) and 15 °C (right). The green dots, lines and dashed lines represent the measured results, the fitted curve and the confidence interval for the Expt A (180 days), respectively, n = 5, with the exception that at 15 °C n = 4 at 28 days, n = 3 at 84 days, n = 4 at 114 days, n = 2 at 170 days). The black dots, lines and dashed lines represent the measured results, the fitted curve and the confidence interval for the experiment B (90-day) (n = 20), respectively. rB: von Bertalanffy growth rate constant. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

systematically adjusted each parameter separately at each temperature (Table S1). Our analysis revealed that changing the kappa (κ) parameter had the best fitting, as indicated by the smallest *AIC* value (Table S1). The adjusted kappa parameter resulted in a better fitting than without any modifications (Fig. 1: A). Hence, we fitted the kappa value to our data and maintained all other parameters at their default values (Table S1). Our results showed that at 11 °C, the kappa (unit as (−)) value was 0.77 (0.74–0.82), and at 15 °C, the value was 0.68 (0.64–0.73). The adjusted model fitted the data better, especially at 15 °C (Fig. 1B), than the unadjusted model (Fig. 1A), with a similar but less pronounced trend observed at 11 °C (Fig. 1B).

Additionally, we calculated the temperature coefficient Q_{10}, which is the factor by which the reaction rate increases when the temperature is raised by ten degrees. Q_{10} is a unitless quantity. In this study, we calculated Q_{10} using Experiment A data at 11 °C ($rB = 0.0045$) and 15 °C ($rB = 0.0058$), resulting in a Q_{10} of 1.89.

3.1.2. *Experiment B: the growth of G. pulex in the 90-day experiment*

At the end of the 90-day experiment, the organisms in the control group at 15 °C grew from 4.6 (±0.3) mm to 8.3 (±0.7) mm, while the organisms in the 11 °C control group grew from 4.4 (±0.4) mm to 7.0 (±1.0) mm. Based on our experimental results, we found that the growth rate increased with higher temperatures (Fig. 2). Also, the sex of organisms was assessed, and the ratio of female to male was about 1:1 in the control treatments of both temperatures (male: female was 9: 9 at 11 °C, and 9:10 at 15 °C). We did not observe any significant differences between the sexes (Fig. S4).

To compare growth rates across different growth experiments, we first fitted the size results of each experiment at the same temperature and found that growth did not differ significantly between the two experiments at the same temperature (Fig. 2). Our findings indicate that the organisms grew faster at higher temperatures, with a growth rate of 0.0038 (0.0034–0.0042) d^{-1} in the Expt B and 0.0045 (0.0041–0.0048) d^{-1} in the Expt A at 11 °C while at 15 °C the growth rates were 0.0056 (0.0052–0.0061) d^{-1} in the Expt B and 0.0058 (0.0051–0.0064) d^{-1} in the Expt A (Fig. 2). At each temperature, the growth rates overlapped between the two experiments (with confidence interval), indicating that there is no noticeable difference in growth between these two experimental conditions.

3.2. *The effects of imidacloprid at different temperatures in the experiment B (90 days)*

The observed effect levels on survival and growth in our study were approximately at the LC_{10} and EC_{10} level. In other words, the effects caused by the highest concentration (0.3 μg/L) resulted in 10% inhibition in both survival and growth compared to the control (support information).

The experiment results were fitted by the DEBtox model (Table 2, Fig. 3). Additionally, we did not detect any significant variations in the *AIC* values across various combinations of modes of action and feedback, as the differences in *AIC* values were less than 3. Nonetheless, we attempted to fit the data using growth costs and classic DEBtox feedback (no losses with reproduction).

For 11 °C and 15 °C, the resulting parameter values were as follows, the confidence interval were listed in Table 2. Regarding the fitting performance, it was acceptable for both temperatures in both lethal and sublethal endpoints. For 11 °C, the fitting efficiency of survival was 0.60, the NRMSE value was 0.060; the fitting efficiency of body length was 0.91, and the NRMSE value was 0.048 (Table 2). For 15 °C, fitting efficiency of survival was 0.52, the NRMSE value was 0.059; the fitting efficiency of body length was 0.98, NRMSE value was 0.026 (Table 2). In summary, the fit for size was better than for survival (Fig. 3). Notably, at 11 °C, due to the less significant differences among treatments, the parameter estimation ran into the lower boundary for the threshold (zb and zs), which resulted in an upper boundary for the effect strength parameter (bb and bs).

In addition, for both Expt A and Expt B, there were no significant differences in sublethal endpoints, such as the head width and dry weight among treatments at each temperature and time point in Expt A ($p > 0.05$). See the SI for more details.

3.3. *The validation of long-term lethal effects*

The calibrated GUTS model predicts a 100d LC_{10} value of 0.30 (0.19–2.4) μg/L for 15 °C and 0.28 (0.20–1.1) for 11 °C (Fig. S7, Fig. S9 and Table S7). Our experimental results were in line with this value since the mortality in our highest treatment (0.3 μg/L) did not exceed 20%. Furthermore, the validation over time matches our current data for the highest treatment (Fig. S8 and Fig. S10). The survival probability prediction error (SPPE) for each treatment was less than 50%, meeting the criteria for model validation as set by the EFSA PPR Panel (Table S7) (EFSA PPR et al., 2018).

4. Discussion

The goal of this study was to assess the impact of pesticides on the survival and growth of *G. pulex* at different temperatures, utilizing both experiments and a DEB modelling approach. Our findings indicate that temperature has a positive effect on the growth rates of *G. pulex*, with faster growth observed at higher temperatures (Figs. 1 and 2). The existing *G. pulex* physiological DEB model has proven to be applicable

Table 2
DEBtox model Calibration Parameter Values.

Temperature (° C)	Parameters value and unit						
	rB	*hb*	*kd*	*zb*	*bb*	*zs*	*bs*
	von Bertalanffy growth rate constant (d^{-1})	background hazard rate (d^{-1})	the dominant rate constant (d^{-1})	effect threshold energy budget ([C])	effect strength energy-budget effect (1/[C])	% effect threshold survival ([C])	effect strength survival (1/([C] d))
11	0.0037 no CIs	0.0018 no CIs	0.013 (0.00033–0.14)	0.19 (0.01–0.29)	215.7 (19.68–1.00E+6)	0.19 (0.01–0.30)	0.17 (0.01–1.00E+6)
15	0.0061 no CIs	0.0011 no CIs	0.0021 (0.0024–0.082)	0.024 (0.016–0.24)	24.35 (1.26–290.40)	0.056 (0.010–0.27)	6.14 (0.0048–4.69)

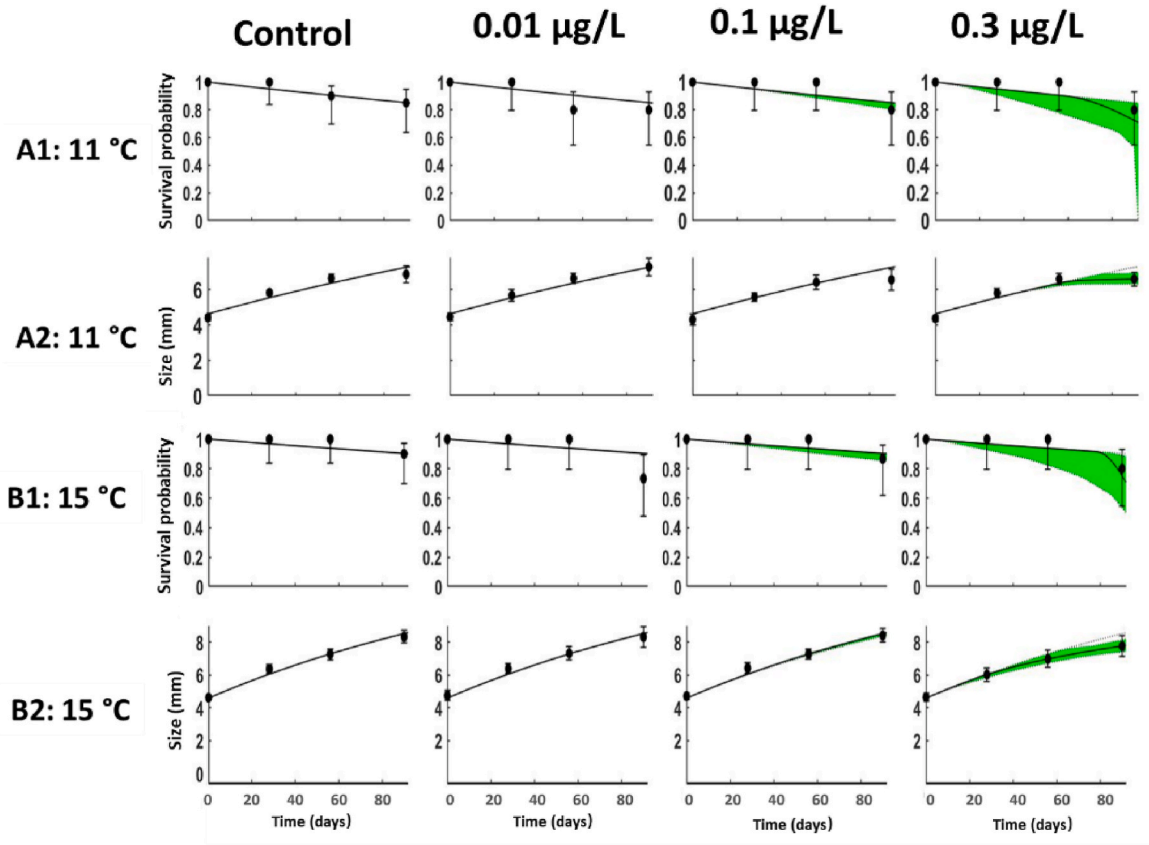

Fig. 3. The survival (A1) and the size (A2) results at 11 °C, and the survival (B1) and the size results (B2) at 15 °C for each treatment in the 90-day experiment. From left to right, data and model calibration in the 0, 0.01, 0.1, and 0.3 µg/L imidacloprid treatments are shown. The dots represent the survival data (A1 or B1) and size data (A2 or B2) from the test; bars represent Wilson score confidence intervals. The line and the green area represent the prediction and the 95 % confidence interval from the model prediction, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Fig. 1). The experimental setup was feasible and repeatable, with consistent results (Fig. 2). The observed effect levels of IMI on survival and growth, under realistic environmental concentration ranges (0.3 µg/L), were around an LC and EC_{10} level (Fig. 3). Nevertheless, the DEB parameter values were calibrated, and indicate differences between temperatures, especially for the intrinsic threshold value (Table 2, zb and zs) which revealed the higher sensitivity at higher temperatures.

4.1. The influence of the temperature on the growth of G. pulex

The growth performance of *G. pulex* in our study exhibited both consistency and replicability, as evidenced by the results depicted in Fig. 2. This underlines the reliability of our experimental setups. Consistent with previous research (Sutcliffe et al., 1981; Moenickes et al., 2011), we found that *G. pulex* demonstrated accelerated growth at higher temperatures, with a Q_{10} value of 1.89. Additionally, we do not need to correct for the initial size of the animals since we use only one growth rate constant for the entire growth period, and there is no life-stage dependent growth.

Our experimental approach demonstrates the efficacy of utilizing adult feces as a food source to facilitate the growth of small juveniles (approximately 2–3 mm). This aligns with previous findings reported by (Kunz et al., 2010). During the juvenile stages, we observed no significant growth rate differences between the sexes, as illustrated in Fig. S4. Sutcliffe et al. (1981), however, showed that male *G. pulex* grows faster than females. It could be due to the shorter experimental duration of our study (90 days), not being long enough to show the difference as in Sutcliffe et al. (1981) the sex difference was not shown until 100 days (Sutcliffe et al., 1981).

Also, our findings provide evidence that the existing physiological *G. pulex* DEB model is capable of representing our experimental data for growth at various temperatures, as demonstrated in Fig. 1. Without any

adjustments, our experimental data aligned with the results of this model to a certain extent, though adjustments did result in a better fit. For instance, the existing DEB model overestimates growth compared to the experimental data, especially between 150 and 200 days at 15 °C, with approximately a 2 mm difference between the unadjusted and adjusted parameters (Fig. 1B). The DEB theory employs the Van't Hoff-Arrhenius equation to depict how physiological rates vary with temperature (Van der Meer, 2006), which can explain the effect of temperature on growth, as shown in Fig. 1. These findings increase our confidence in using DEB parameters to predict species growth at different temperatures. Extremely high temperatures may, however, also inhibit the growth or even cause lethal effects when the temperature is out of the species' thermal tolerance.

More refined, our results indicate that adjusting the kappa parameter leads to improved fitting for each experimented temperature (Fig. 1 and Table S1). Kappa (κ) represents the energy allocated to somatic maintenance and growth and is a fixed fraction of energy mobilized from the reserve. The remainder of mobilized energy (1-kappa) is allocated to either maturation (juveniles) or reproduction (adults). The parameter kappa can be influenced by the animals' stressors, such as toxins and temperatures (Nisbet, 1995). Our results of a lower kappa at a higher temperature indicated a higher maturation or reproduction at a higher temperature. Additionally, since Gammarus reach adulthood at a specific size, but not the maximum length, it is reasonable to assume that reproduction rates could be higher and begin earlier in warmer conditions. Future studies could explore this hypothesis further.

4.2. The effects of imidacloprid on the survival and growth of G. pulex

4.2.1. Results of the 90-day experiment

The effects caused by the highest concentration (0.3 μg/L) resulted in 10% inhibition in both survival and growth compared to the control group (Table 2, Fig. 3) was unexpected. We initially hypothesized that IMI would have a more significant impact on the feeding or mobility of *G. pulex*, thus affecting its growth at a concentration lower than what would be lethal, in line with previous studies which also studied the effect of IMI on *G. pulex*. For instance, Agatz et al. (2014) found that sublethal effect values were lower than lethal effects, they observed effects of IMI on feeding rate at concentrations two orders of magnitude lower than those causing mortality. Specifically, they reported an LC_{50} of 270 μg/L after 4 days of exposure, compared to an EC_{50} of 5.34 μg/L (Agatz et al., 2014). Another study reported an LC_{10} of 0.1 μg/L and an EC_{10} (affecting mobility) of 0.03 μg/L after 28 days of exposure (Huang et al., 2023). In our longer term exposure experiment (duration 90 days), we expected a more distinct separation between mortality and sublethal effects but our findings did not conform to this expectation. In our study low (environmentally realistic concentrations) were used to see if effects on growth would occur. But the organisms were fed ad-libitum, which may disguise effects on growth.

Another more speculative explanation is that different mechanisms may be at play under varying concentrations. In cases of higher chemical exposure, as observed in previous studies (Agatz et al., 2014; Huang et al., 2023), the chemical might inhibit feeding activity or mobility, eventually leading to death. This could result in a lower effective concentration (EC) value compared to the lethal concentration (LC) value. However, at the lower exposure levels used in our study, the mechanisms can be different. While the specifics remain unclear, we observed no significant difference in LC or ECx values between lethal and sublethal effects under low chemical exposure. This suggests that the differences between lethal and sublethal effects are not solely dependent on the tested chemicals and species but may also be influenced by the exposure concentrations. Again, this is speculative, but we do highlight the importance of conducting more research on low environmentally relevant concentrations, rather than focusing solely on acute high-concentration exposures, to better understand more realistic effects.

4.2.2. The DEB model calibration

While the experimental data did not reach statistical significance, a consistent trend emerged towards the end of the treatment, showing that the effects became more pronounced with higher concentrations over time (Fig. 3). It is important to interpret these effects with caution since the observed effect levels were around the EC_{10} levels. The value of the parameter effect strength (both bb and bs) at 11 °C was difficult to pinpoint, as in the estimation procedure the value moved towards infinity, leading to large confidence intervals for all parameter values (Table 2). The lethal threshold value (zs) at 15 °C (0.056, CIs: 0.010–0.27 μg/L) was lower than that at 11 °C (0.19, CIs: 0.01–0.30 μg/L), and similarly, the sublethal threshold value (zb) at 15 °C (0.024, CIs: 0.016–0.24 μg/L) was lower than at 11 °C (0.19, CIs: 0.01–0.29 μg/L). These findings suggest an elevated intrinsic sensitivity of organisms at higher temperatures (Table 2). The threshold level reflects intrinsic sensitivity; once the external concentration exceeds this value, effects begin to accumulate. Our results show that this value is lower at higher temperatures, indicating that animals are more susceptible to adverse effects at higher temperature. A closer examination of the results at 15 °C reveals that the zb value is lower than the zs value, indicating that the observed effects initially manifested at the sublethal level before progressing to the lethal level, as previously discussed by (Gergs et al., 2021).

To the extent of our understanding, only a few studies were found in the literature that have determined the relationship between GUTS parameters with temperatures (Gergs et al., 2019; Mangold-Doring et al., 2022; Huang et al., 2023). In the study by Gergs et al. (2019), acute toxicity tests were conducted over a period of 96 h to evaluate the toxicity of chlorpyrifos to *Daphnia magna* at different temperatures. The findings revealed that as temperatures increased, both the dominant rate and effect strength of chlorpyrifos toxicity increased, while the threshold remained independent of temperature (Gergs et al., 2019). In another study by Mangold-Doring et al. (2022), temperature-dependent toxicokinetic and toxicodynamic models were developed for *G. pulex*. That study investigated the impact of temperature on various toxicokinetic and toxicodynamic aspects. For the toxicokinetic part, the uptake rate constant and elimination rate of imidacloprid were found to be higher at higher temperatures. Additionally, the toxicodynamic model parameters were also influenced by temperature (Mangold-Doring et al., 2022) in line with the findings of Gergs et al. (2019).

There is still limited knowledge regarding the impact of temperature on sublethal effects in long-term tests, particularly when utilizing the DEB model to gain a mechanistic understanding. Consequently, the DEB parameters we have calibrated provide a valuable resource, offering insights that can guide future research endeavors.

4.3. Reflections and recommendation

This study aimed to model the effects of pesticides on the life cycle of an aquatic crustacean, specifically growth without reproduction, at different temperatures. Our experimental design successfully accommodated multiple time points to suit the calibration requirements of the Dynamic Energy Budget (DEB) model. We employed two experimental designs, each with unique merits and demerits. While the non-destructive design allowed us to monitor the growth of the same individual and determine their sex over time, which increased the statistical power of the analyses, it was time-consuming. We suggest that carbon dioxide or other chemicals could be used to paralyse the animals to improve the non-destructive size measurement efficiency, although the potential effects of these anaesthetics need evaluation (Wahltinez et al., 2022). Conversely, the destructive design required a larger initial sample size but became more efficient over time. From a practical perspective, this approach saves time, yet measuring different individuals on each occasion introduces some degree of imprecision compared to the non-destructive design. Overall, both methods are acceptable, and future studies should consider these factors while

designing experiments to evaluate pesticides' effects on crustaceans at different temperatures.

Additionally, modelling proves valuable for data interpretation and extension. The DEB model effectively interprets the experimental data with chemicals, as demonstrated (Table 2 , Fig. 3). Our experimental setup greatly enhances data acquisition, aiding the DEB model's application to *G. pulex* in assessing responses to various chemicals and temperature changes. The model's parameterization revealed subtle data differences, illuminating underlying mechanisms, such as the lower threshold value, which indicates higher intrinsic sensitivity at higher temperatures. Noted, this study focused on calibration to reveal the impact of temperature on chemical influence, laying the groundwork for future validation studies, possibly including pulse exposure scenarios. Moreover, we employed existing data and successfully validated our long-term findings concerning mortality using shorter-term observations. The validation process yielded good results, allowing us to establish a connection between two independent datasets (Figure S7-S10). But we also acknowledge the limitation in our study that due to the small magnitude (LC and EC_{10} levels) of both lethal and sublethal effects, we need to be cautious about its interpretation.

Reflecting on our study and past research, it is indicated that higher IMI concentrations might have more noticeable effects on *G. pulex*. Huang et al. (2023) observed that at 10 μg/L, over 28 days at 15 °C, *G. pulex*'s dry weight was lower than the control group's, though not significantly, possibly due to high individual variances (Huang et al., 2023). Similarly, Agatz et al. (2014) noted a significant 50% reduction in *G. pulex*'s food consumption at 5.34 μg/L IMI after 4 days (Agatz et al., 2014). Therefore, concentrations around 5 or 10 μg/L could lead to more distinct outcomes. But our study focused on the realistic environmental concentrations of IMI, particularly relevant since its outdoor usage in Europe was banned in 2018. The measured environmental concentrations of IMI range from ng/L to approximately 10 μg/L (Hladik et al., 2018; Pietrzak et al., 2019), and the environmental concentration was expected to be lower after 2018. For example, a recent study detected IMI in Spain's Tagus River basin, with a range of 23–700 ng/L and an average of 130 ng/L in the Ebro River Delta, Spain (Barbieri et al., 2021). Another study in Spain detected IMI at an average concentration of 2.75 ng/L in surface water (Casillas et al., 2022).

Additionally, we selected temperatures that realistically represent conditions in the Netherlands, with 11 °C as the common ambient temperature (Thunnissen et al., 2020) and a 4 °C increase to simulate warmer scenarios. These selections reflect practical conditions for our study, but sites with higher ambient temperatures or detected chemical concentrations should consider more specific, realistic scenarios.

In conclusion, our findings hold significant value for future research endeavours focused on exploring the effects of environmental contaminants on aquatic organisms and ecosystem health, with a particular emphasis on long-term effects and climate change, aiming to protect biodiversity (Polazzo et al., 2022).

5. Conclusion

Our study aimed to assess the impact of environmental concentrations of imidacloprid on the growth and survival of *G. pulex* at two different temperatures. Moreover, we aimed to elucidate the underlying mechanisms linking toxicity and temperature, employing a Dynamic Energy Budget (DEB) model for this purpose. Our results reveal that the environmental concentration of IMI (up to 0.3 μg/L) has limited effects on the mortality and growth of *G. pulex* after a 3 months or 6 months exposure. After successfully parameterizing the DEB model at various temperatures, we identified a lower threshold value for both lethal and sublethal effects at higher temperatures, suggesting higher intrinsic sensitivity at higher temperatures. However, we acknowledge the limitations of our study due to the limited observable effects, emphasizing the need for cautious interpretation of the model parameters. Additionally, the growth of control group animals remained consistent across two separate experiments, affirming the practicality of utilizing small juveniles in our study. Overall, this research contributes to future risk assessments that consider temperature as a pivotal factor and exemplifies the integration of the DEB model into the experimental design for comprehensive toxicity evaluations.

CRediT authorship contribution statement

Anna Huang: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Paul J. Van den Brink:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Nico W. Van den Brink:** Writing – review & editing, Supervision, Conceptualization. **Jan Baas:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

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.

Data availability

The raw data regarding the growth of *G. pulex* is provided in the Mendeley repository DOI: 10.17632/69hbywn6vx.1

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2024.142511.

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