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Implications of inhalation bioaccessibility for the exposure assessment of drifting airborne pesticides caused by field spraying

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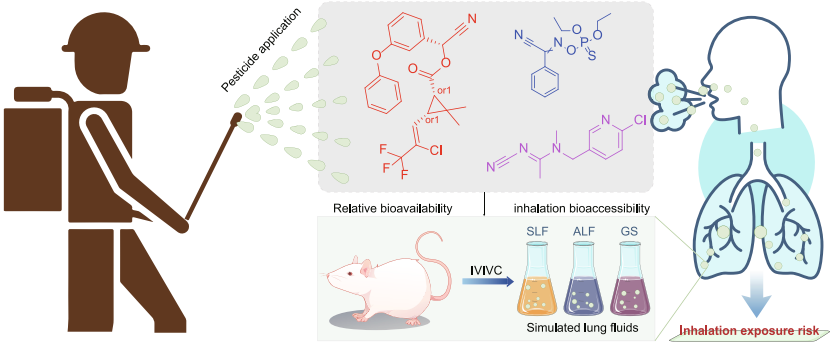
HIGHLIGHTS

- Inhalation exposure to airborne pesticides during application and post-application was investigated.
- Pesticide UEs were observed to be significantly affected by spraying nozzles and formulations.
- An *in vitro* method to estimate pesticide inhalation bioaccessibility was developed based on IVIVC.
- ADD of inhalation exposure calculated after incorporating bioaccessibility decreased by >32 %.

GRAPHICAL ABSTRACT



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ABSTRACT

Pesticide contamination in ambient air due to spray drifting has received extensive attention. Quantifying the associated health risk highlights the importance of incorporating bioaccessibility into inhalation exposure assessments rather than using the total inhaled concentration of airborne pesticides. In this study, we measured the inhalation unit exposure (UE) of three typical pesticides (lambda-cyhalothrin, phoxim, and acetamiprid) during application and post-application drift at the recommended application dosage. The UE values were found to be 1.74–424.37 ng/m^3 and 0.07–1.40 ng/m^3, respectively, with marked variation between different spraying nozzles and formulations. For the inhalation exposure assessment, an *in vitro* method was developed to determine the inhalation bioaccessibility of lambda-cyhalothrin, phoxim, and acetamiprid and its applicability was validated based on *in vivo-in vitro* correlations (IVIVC) analysis. Their conservative inhalation bioaccessibility values estimates were 46.09 %, 67.12 %, and 40.31 %, respectively. The calculated average daily dose values of the analyzed pesticides in both single and mixed formulations ranged from 8.03×10^{-8} to 4.35×10^{-5} mg/kg·day based on the bioaccessible UE, corresponding to 22.99–67.11 % of the total exposure. Collectively, these findings are of guiding significance for improving risk management in pesticide application.

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1. Introduction

Pesticides are important chemicals or biological agents that are widely employed to manage pests in agriculture. It has been estimated that global pesticide usage reaches 2.7 million metric tons annually (Chen et al., 2024a). Spraying is the most common method of pesticide application; however, spraying may result in 30–50 % of the sprayed amount being lost to the ambient air through spray drifting and post-application volatilization (Zhao et al., 2023). Moreover, pesticide formulations frequently contain several active ingredients to improve their efficacy during field application, resulting in air contamination with multiple pesticides (de Souza Guida et al., 2018). As a result, there is growing concern about the adverse effects of airborne pesticides from field spraying on human health.

The potential health risk of environmental pollutants depend on their inherent toxicity and actual inhaled exposure dose. Generally, the assessment of the inhalation exposure concentrations of airborne pesticides is based on the unit exposure (UE), which is derived through the collection of pesticide residues in ambient air using air samplers (Cao et al., 2018). However, to exert a negative health impact on the human body, the inhaled pesticides must be able to dissolve in lung fluids and be absorbed into the systemic circulation (Liu et al., 2024). Studies on bioaccessibility (Xie et al., 2018) and bioavailability (Kastury et al., 2017) have indicated that only a portion of inhaled contaminants are ultimately bioavailable to humans. Consequently, studies have increasingly highlighted the importance of incorporating bioaccessibility or bioavailability into inhalation exposure assessment to avoid overestimation associated with the use of the total inhaled concentrations (Liu et al., 2019a). To the best of our knowledge, inhalation bioaccessibility and bioavailability have been employed to evaluate heavy metals (Zupančič et al., 2024), polycyclic aromatic hydrocarbons (Xie et al., 2018), and dust or particulate matter (Gao et al., 2018). However, to date, the inhalation bioaccessibility of airborne pesticides has rarely been studied.

Bioavailability, which represents the fraction absorbed in systemic blood circulation, is generally measured following *in-vivo* methods that utilize animal models (Dima et al., 2020). However, ethical concerns and time costs make *in-vivo* assays unsuitable for routine testing. As a conservative estimate, *in-vitro* inhalation bioaccessibility assays have recently been developed because of their cost-effectiveness and lower time requirements (Li et al., 2019). Existing *in-vitro* methods have been widely employed in inhalation bioaccessibility research on nanoparticles (Jalink et al., 2020) and heavy metals (Huang et al., 2018). Notably, these methods utilized physiologically based extraction tests using simulated lung fluids, which may have a significant impact on the results due to methodological differences (Wei et al., 2018). For example, Kastury et al. (2017) reviewed how variability in methodological parameters led to significant differences in the inhalation bioaccessibility outcomes of metals in ambient particulate matter and dust (Kastury et al., 2017). Therefore, the establishment of validated *in vivo-in vitro* correlations (IVIVC) is particularly important for validating the applicability of inhalation bioaccessibility assays (Liu et al., 2023).

Accordingly, this study optimized and validated an *in-vitro* method to measure the inhalation bioaccessibility of three typical pesticides, namely, phoxim, acetamiprid, and lambda-cyhalothrin, using response surface methodology (RSM) and the IVIVC. Moreover, we evaluated the inhalation exposure level to the analyzed pesticides in both single and mixed formulations during pesticide application and post-application drift, incorporating inhalation bioaccessibility adjustments to better guide risk management.

2. Materials and methods

2.1. Chemicals and sample preparation

Pesticide standards of phoxim, acetamiprid, and lambda-cyhalothrin were obtained from Dr. Ehrenstorfer GmbH (purity ≥98.2 %; Augsburg, Germany). The commercial formulations of phoxim, acetamiprid, and lambda-cyhalothrin produced by relevant pesticide factories are summarized in Table S1. The compositions of simulated lung fluids, including Gamble's solution (GS; to mimic the intercellular fluid deep within the lung), artificial lysosomal fluid (ALF, to simulate the acidic intracellular environment of the lung macrophage lysosome), and surrogate lung fluid (SLF, to mimic the key interface between the human respiratory tract and inhaled air), were provided and prepared according our previous study (Xiao et al., 2023).

2.2. Field trials and inhalation exposure

The experiment was conducted in a cotton field located in Feixi city, Anhui province, China. During the field trials, there was no other pesticide application activities within 2 km of the test farmland. Climatic conditions recorded using a weather meter showed an average temperature of 29.8 °C, a wind velocity of 0.3 m/s and a relative humidity of 33.2 %.

For pesticide application, the 5 % lambda-cyhalothrin emulsion (EW), 20 % acetamiprid soluble concentrate (SL), 40 % phoxim emulsifiable concentrate (EC), 26 % lambda-cyhalothrin·acetamiprid water dispersible granule (WG), and 20 % lambda-cyhalothrin· phoxim EC were sprayed manually at 15 g a.i./ha, 15 g a.i./ha, 300 g a.i./ha, 19.5 g a.i./ha, 300 g a.i./ha (recommended dosage) in each separate experimental plot, respectively. The spraying equipment used consisted of a traditional electric air-pressure knapsack (EAP) sprayer at a working pressure of 0.15–0.40 MPa, and the volume of each spraying was 30 L.

For inhalation exposure, a QS-1S personal air sampler equipped with an XAD-2 sorbent tube was positioned in the breathing zone of the applicator to collect ambient air during pesticide application. The sampling was conducted at a gas flow rate of 1 L/min for a duration of 20 m. Meanwhile, a KC-120H medium-flow size-grading sampler equipped with a glass fiber filter (thickness 0.3 μm; diameter 90 mm) was installed 50 m downwind at the field to collect airborne pesticides during post-application drift. The sampling head was 1.5 m above the ground, and ambient air samples were collected for 2 h at a flow rate of 100 L/min. Each treatment consisted of four replicate plots, and a 0.5 km buffer zone was set among plots to avoid the effects of droplet drift pollution. After collection, the sampling medium was wrapped immediately with aluminum foil and maintained at −20 °C until pesticide analysis.

2.3. In-vitro inhalation bioaccessibility assays

In this study, the inhalation bioaccessibility of the selected pesticides was investigated using three commonly used *in-vitro* procedures (GS, ALF, and SLF). Briefly, the air sampling medium was added to 20 mL of the simulated lung fluids, followed by the lung simulation procedure in accordance with our previous study (Xiao et al., 2023). The detailed *in vitro* procedures are presented in Supporting information. The value of inhalation bioaccessibility (BA, %) was calculated as follows:

$$BA\ (\%) = \frac{C_1 \times V_1}{C_2 \times M} \times 100\%$$

where C_1 is the concentration of pesticide in the lung fluid (mg/L), V_1 is the volume of lung fluid (mL), C_2 is the concentration of pesticide in the

air sampling medium (mg/kg), and *M* is the mass of the air sampling medium (mg).

2.4. RSM analysis

The variations in the following parameters of the *in-vitro* inhalation bioaccessibility procedures were modeled to identify the appropriate conditions: the extraction duration (0.5, 1, 2, 6, and 12 h), the solid−liquid ratio (*S/L*; 1/2000, 1/1500, 1/1000, 1/500, 1/250, and /1/100), and the agitation (50, 100, and 150 r/min). Afterward, RSM based on Box–Behnken design (Design Expert 13, Stat-Ease Inc., Minneapolis MN, USA) was employed for further experimental design. In this approach, the predictor variables were employed as the extraction duration (A), *S/L* (B), and agitation (C) were applied as predictor variables, while inhalation bioaccessibility (Y) was identified as the response variable.

2.5. In-vivo animal bioassay

Using an *in vivo* mouse bioassay, the relative bioavailability of the analyzed pesticides was estimated in order to validate the *in-vitro* inhalation bioaccessibility outcome. Briefly, female BALB/c mice were acclimated under a standard animal housing condition for 1 week. Food and water were available *ad libitum*. Following acclimation, animals ($n = 6$/group) were intranasally instilled with 0.2 mL of 0.9 % sterile saline containing the tested pesticides (50 mg/L), and the calculated inhalable dose for mice was 0.05 mg/kg·bw. Control mice ($n = 6$/group) were injected intravenously in the tail at the same dose for the tested pesticides. After pesticide exposure, each mouse was individually housed in a standard laboratory cage and blood samples were collected at 0.5, 1, 2, 6, 12, and 24 h using a heparin tube. Plasma was obtained by centrifuging the collected samples at 8000 $\times g$ for 5 min. Subsequently, the pharmacokinetic analyses were conducted in PK solver 2.0 using a noncompartmental method (Zhang et al., 2010). The relative bioavailability was defined as the ratio of the mean area under the concentration *versus* the time curve obtained in the intranasal instillation treatment to that of intravenous injection treatment, and the values (%) were calculated using the formula described in our previous study (Xiao et al., 2023).

2.6. IVIVC model

The inhalation bioaccessibility procedures were validated and optimized *via* IVIVC. The linear regression relationship with the inclusion of 95 % confidence between the *in-vitro* inhalation bioaccessibility data and the *in-vivo* relative bioavailability data was fitted using R (version 4.2; R Development Core Team). The criteria used to verify the reliability of the *in-vitro* assays were in accordance with Li et al. (2016).

2.7. Sample analysis and quality control

The sample extraction and purification procedures were performed following the QuEChERS method with modifications. Details about the pesticide residue analysis and quality control were provided in the Supporting information. Method validation was carried out with respect to linearity, matrix effect (ME), accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ), which are summarized in Table S2.

2.8. Estimation of human exposure

Human exposure to pesticides *via* inhalation was estimated based on the average daily dose (ADD_{inh}, mg/kg·day), which was calculated using a model based on the United States Environmental Protection Agency (EPA) guidelines for exposure assessment (Authority, 2014). Details about the equation were provided in the Supporting information.

3. Results and discussion

3.1. Inhalation unit exposure

The size of spray droplets is a crucial factor influencing spray drift (Chen et al., 2020). This study investigated the effect of two types of nozzles (single-hole cone type: 160 μm of volume median diameter; twin-hole cone type: 190 μm of volume median diameter) on the inhalation UE of the active ingredient during pesticide application. As expected, it was observed that there was a positive correlation between inhalation UE and spray droplet size (Fig. 1). Briefly, the inhalation UEs of the active ingredients of 5 % lambda-cyhalothrin EW, 20 % acetamiprid SL, and 40 % phoxim EC sprayed using the single-hole nozzles were 152.01 ng/m^3, 1.74 ng/m^3, and 17.08 ng/m^3 under the recommended application dosages, respectively. By contrast, higher values were found using twin-hole nozzle spraying, with UE values of 424.37 ng/m^3, 2.52 ng/m^3, and 35.49 ng/m^3 for 5 % lambda-cyhalothrin EW, 20 % acetamiprid SL, and 40 % phoxim EC, respectively. The airborne pesticide concentrations of the EW formulation were higher than the concentrations for the SL and EC formulations, which may be interpreted as the effect on the droplet size and particle size distribution caused by the pesticide formulation (Carvalho et al., 2017). Studies have indicated that the smaller the spray droplets, the longer the pesticides remain in the air (Xue et al., 2021). Interestingly, an opposite trend was observed when comparing the effect of pesticide formulation on the concentrations of airborne pesticide at 50 m downwind of the field within 2 h after application. Measurements showed that the inhalation UEs of the active ingredients of 5 % lambda-cyhalothrin EW, 20 % acetamiprid SL, and 40 % phoxim EC were 0.07 ng/m^3, 0.82 ng/m^3, and 0.79 ng/m^3, respectively, which could be attributed to the relatively small droplets easily drifting over long distances in the wind (Wang et al., 2020).

Pesticide formulations frequently contain several active ingredients aimed at managing resistance and broadening the spectrum of pest control (Hazra and Purkait, 2019). Monitoring pesticide residues has revealed the presence of complex pesticide mixtures in ambient air samples, rousing increasing concern about the effects of these mixtures on human health (Coscollà et al., 2017). Therefore, this study further measured the inhalation UEs of the mixed active ingredients of 26 % lambda-cyhalothrin·acetamiprid WG and 20 % lambda-cyhalothrin·phoxim EC. The inhalation UEs of 26 % lambda-cyhalothrin·acetamiprid WG using single-hole nozzles and twin-hole nozzle spraying were 142.53 ng/m^3 and 134.48 ng/m^3, respectively, with corresponding values of 115.96 ng/m^3 and 141.62 ng/m^3 for 20 % lambda-cyhalothrin·phoxim EC applied using single-hole nozzles and twin-hole nozzle spraying, respectively. Notably, the mixed pesticide formulations exhibited relatively higher UE during post-application drift, with values ranging from 0.31 ng/m^3 to 1.40 ng/m^3 under the recommended application dosages. The results suggest that the drift risk of active ingredients in mixed pesticide formulations is relatively high, which may be was possibly caused by a combination effect, including active ingredient content, pesticide dissipation rates (University of Hertfordshire, 2021), and adjuvants (Zeeshan et al., 2024).

3.2. Influences on the methodology for assessing inhalation bioaccessibility

Previous studies have demonstrated that variations in parameters such as the extraction duration, *S/L* ratio, and agitation can produce large variability in the bioaccessibility outcomes of heavy metals (Hernández-Pellón et al., 2018) and polycyclic aromatic hydrocarbons (Sánchez-Piñero et al., 2021). Thus, methodological factors were investigated in order to develop an *in vitro* method to test the inhalation bioaccessibility of pesticides using simulated lung fluids.

The extraction duration is related to the particle residence time for inhalation exposure (Weggeberg et al., 2019). In the present study, the

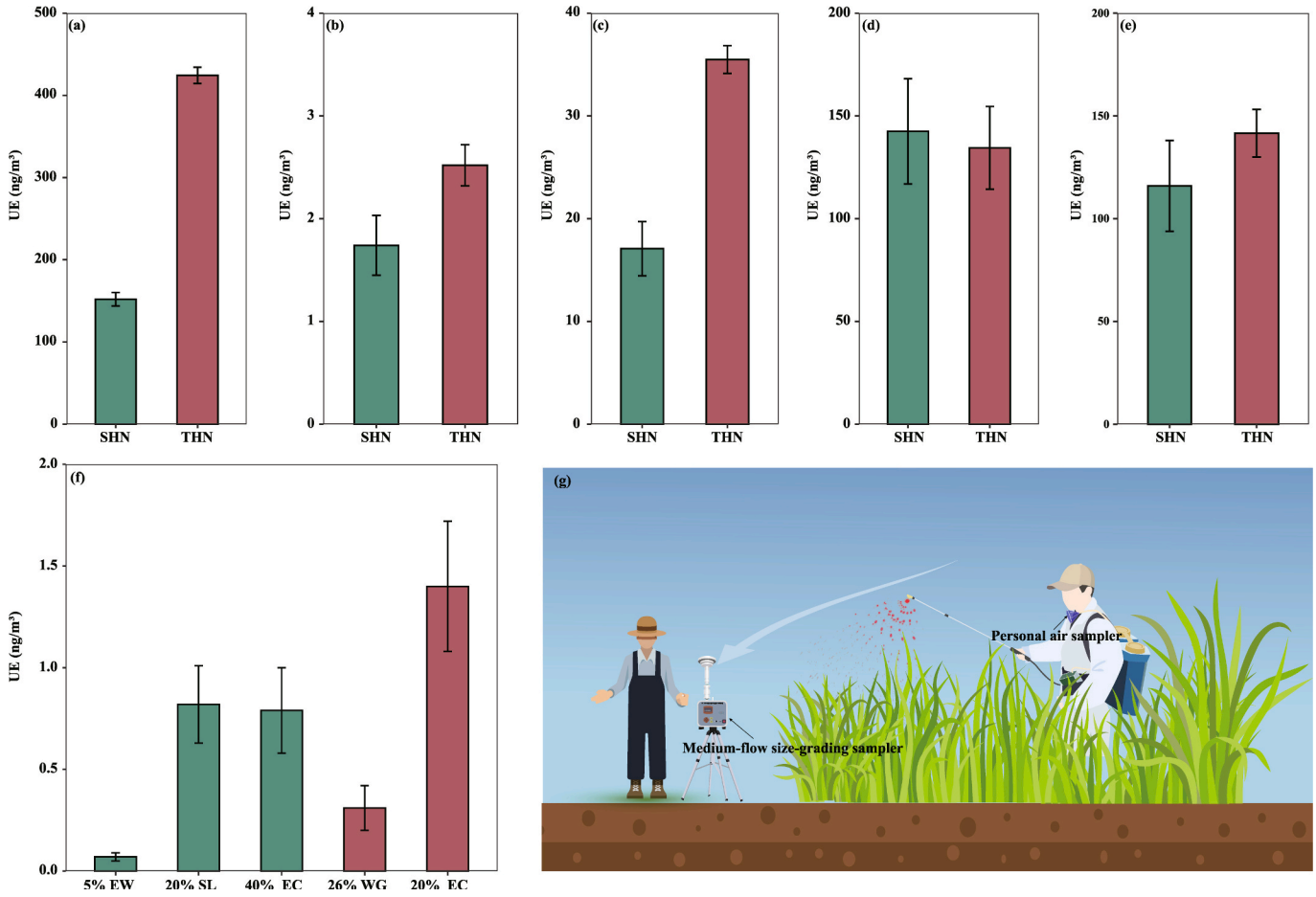

Fig. 1. Inhalation UEs of 5 % lambda-cyhalothrin EW (a; 5 % EW), 20 % acetamiprid SL (b; 20 % SL), and 40 % phoxim EC (c; 40 % EC), 26 % lambda-cyhalothrin·acetamiprid WG (d; 26 % WG), and 20 % lambda-cyhalothrin·phoxim EC (e; 20 % EC) measured for handheld spraying and post-application drift (f). For inhalation exposure, a personal air sampler with an XAD-2 sorbent tube was used to collect ambient air during pesticide spraying, and a medium-flow size-grading sampler equipped with a glass fiber filter was located downwind of the experimental field at a distance of 50 m to quantitatively capture pesticides drifting into the nearby area after pesticide post-application (g). SHN and THN represent single-hole nozzles and twin-hole nozzles, respectively.

timeframe (0.5–12 h) for inhalation bioaccessibility studies indicated that the release of the analyzed pesticides into the simulated lung fluid occurred rapidly during the initial hours and then asymptotically approached equilibrium at 12 h (Fig. 2a), suggesting that this timeframe is sufficient for the bioaccessibility assessment. The time-dependence of inhalation bioaccessibility exhibited a strong logarithmic relationship, with an R^2 value of >0.78. At equilibrium (12*h*), the inhalation bioaccessibility values of lambda-cyhalothrin were 75.36 %, 40.77 %, and 49.53 % using GS, ALF, and SLF, respectively; that of acetamiprid was 72.09 %, 54.97 %, and 56.43 % and for phoxim was 57.54 %, 56.95 %, and 40.31 %. The analyzed pesticides exhibited relatively high bioaccessibility in GS, which agreed with the findings of Liu et al. (2019b). This may be due to the differences in fluid composition with respect to chelation capacity, resulting in a higher extraction efficiency for GS (Xie et al., 2018). The observed result implies that the dissolved pesticides can potentially be absorbed into the systemic circulation *via* the intercellular fluid, warranting further investigation (Chen et al., 2024b).

For inhalation bioaccessibility studies, *S/L* ratio parameter is considered to be the concentration of pollutants breathed into lung fluid (Besis et al., 2022). The inhalation bioaccessibility of the analyzed pesticides showed an overall decreasing trend as the *S/L* ratio increased (Fig. 2b). Lambda-cyhalothrin, acetamiprid, and phoxim reached maximum values of 76.25–77.98 %, 22.32–56.77 %, and 32.46–64.25 % at an *S/L* ratio of 1/2000, respectively. The reduction was probably due to the decreased absorptivity of sampling medium and subsequent effect on the release efficiency (Expósito et al., 2021).

Agitation also plays a major role in preventing particle agglomeration and increasing substance solubility (Kastury et al., 2018a). Similarly, a statistically significant increase in inhalation bioaccessibility was observed as the agitation speed increased (Fig. 2c). The value of inhalation bioaccessibility increased from 8.35 to 38.60 % at an agitation speed of 50 r/min to 14.33–65.18 % at an agitation speed of 150 r/min. The impact of mechanical agitation was similar to that reported in several inhalation bioaccessibility studies on loids (Kastury et al., 2018b) and PAHs (Ren et al., 2020).

3.3. RSM analysis of influencing factors

The interactive effects among the methodological factors on the inhalation bioaccessibility outcomes were investigated using an RSM approach in this study. As shown in Tables S3–5, the high R^2 (0.8731–0.9983), *F*-value (5.35–462.86), and lack-of-fit (4.32–74.64) values suggested that the experimental data were well fitted with the model (Zhang and Li, 2019). Moreover, it is generally the interaction term between extraction duration and *S/L* ratio that has the greatest impact on inhalation bioaccessibility. The RSM analysis showed that the inhalation bioaccessibility of lambda-cyhalothrin using SLF reached the maximum point at an extraction time of 22 h, an *S/L* ratio of 1/1000, and agitation of 250 r/min; for phoxim, the maximum inhalation bioaccessibility was observed at an extraction time of 24 h, an *S/L* ratio of 1/1000, and agitation of 210 r/min; and for acetamiprid, the maximum inhalation bioaccessibility occurred at an extraction time of 21 h, an *S/L*

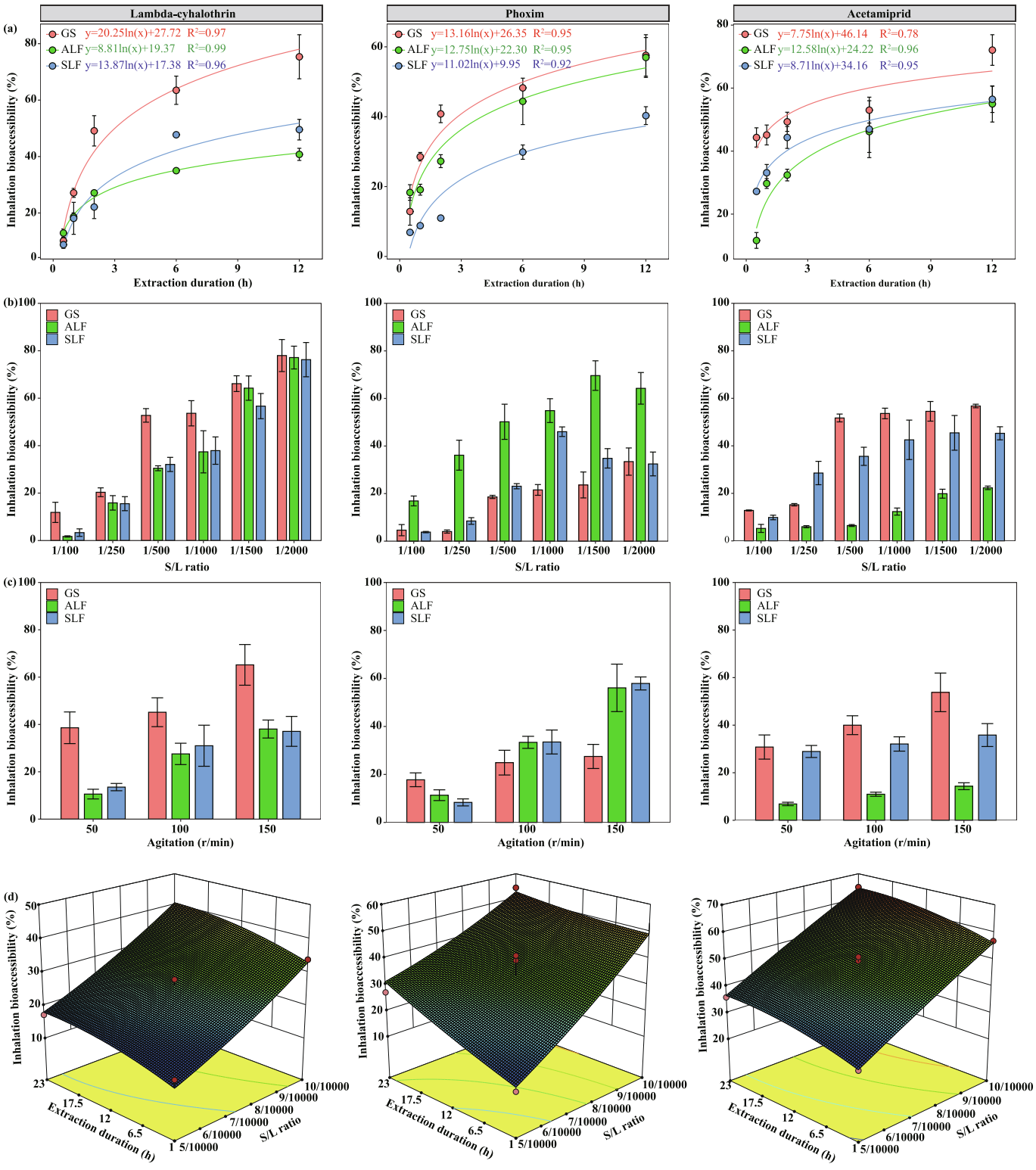

Fig. 2. Impact of the extraction time (a), S/L ratio (b), and agitation (c) on the inhalation bioaccessibility of emamectin benzoate in different simulated lung fluids. Response surface showing the interactive effects among the methodological factors on the inhalation bioaccessibility outcomes (d).

ratio of 1/1000, and agitation of 50 r/min (Fig. 2d). Under the methodological parameters, the experimental inhalation bioaccessibility of lambda-cyhalothrin, phoxim, and acetamiprid reached 45.85 %, 65.11 %, and 67.14 %, respectively.

3.4. *In-vivo* determination of relative bioavailability

Bioavailable chemicals inhaled into the lungs enter the blood circulatory system directly (Kastury et al., 2019). Therefore, in the present study, the mouse plasma area under the concentration–time curve (AUC) of the analyzed pesticides was used as the end point for the *in-vivo* relative inhalation bioavailability assessment. The AUC profiles for

intranasal instillation and intravenous injection treatment based on pharmacokinetic analysis are shown in Fig. 3, and the corresponding pharmacokinetic parameters are summarized in Table S6. We observed that acetamiprid was rapidly absorbed into the blood circulatory system, reaching the maximum plasma concentration (C_{max}) after 0.5 h (T_{max}), and the T_{max} value for both lambda-cyhalothrin and phoxim was 2 h. The terminal half-life ($T_{1/2}$) values of lambda-cyhalothrin, phoxim, and acetamiprid after intranasal instillation exposure were 10.00 h, 6.08 h, and 3.66 h, respectively. A similar systemic clearance by both routes was indicated by these values, which were essentially comparable to those obtained after intravenous injection (Mehvar, 2018). The area under the curve to the last measurable time point (AUC_{last}) and to infinity ($AUC_{0-\infty}$) for both intranasal instillation and intravenous injection exposure were > 80 % for the analyzed pesticides, demonstrating an appropriate duration for pharmacokinetic analysis (Neely et al., 2018). Consequently, based on the pharmacokinetic profiles within 24 h of exposure, the relative bioavailability values of lambda-cyhalothrin, phoxim, and acetamiprid were determined to be 46.09 %, 67.12 %, and 40.31 %, respectively.

3.5. IVIVC analysis

Based on the *in-vivo* animal bioassay results, which indicated that 24 h of exposure was suitable for calculating the relative bioavailability in this study, a 24-h extraction duration is therefore recommended when performing inhalation bioaccessibility assessments according to this method. RSM analysis of the influencing factors showed that the interaction between the extraction duration and the *S/L* ratio generally had the greatest effect on inhalation bioaccessibility. The value of the *S/L* ratio has been loosely selected in many studies, with values ranging widely from 1/100 to 1/5000. To evaluate the reliability of the *in-vitro* method with an *S/L* ratio of 1/1000, this study established an IVIVC of the inhalation bioaccessibility for the corresponding *in-vitro* procedures with the relative bioavailability in mice based on five spiked concentrations. As shown in Fig. 4, satisfactory linearity was observed between the inhalation bioaccessibility and the relative bioavailability of lambda-cyhalothrin, phoxim, and acetamiprid, with correlation coefficients (r^2) of 0.8248, 0.8595, and 0.7715, respectively, and corresponding linear slope values of 0.72, 0.70, and 1.18, respectively. The laboratory and between-laboratory repeatability obtained with relative standard deviations (RSDs) ranged from 4.82 to 9.37 %. The correlation met the criteria of $r^2 > 0.60$, slope of 0.8–1.2, and RSD < 10 %, suggesting that the *in-vitro* method with an *S/L* ratio of 1/1000 can be used to estimate the inhalation bioaccessibility of the analyzed pesticides. Consequently, the findings of this study suggest that the optimized SLF, at an *S/L* ratio of 1/1000, extraction duration of 24 h, and agitation of 200 r/min, can be recommended. Moreover, previous studies on IVIVC have found that the physicochemical properties of the environmental medium, including the particle size distribution (Li et al., 2021) and organic carbon contents (Shi et al., 2023) of dust and aerosols, are important parameters for bioaccessibility and bioavailability. The feasibility of this method for predicting the relative bioavailability should be validated with a wider range of matrices in future research.

3.6. Inhalation bioaccessibility-based risk assessment

Mixed pesticide formulations may contribute greatly to pesticide inhalation exposure and increase the potential health risks (Nagy et al., 2020). Thus, the ADD values of different formulations were estimated to compare the exposure risk between single pesticide formulations and mixed formulations (Table 1). To the best of our knowledge, this study provides the first evidence that mixed pesticide formulations may increase the risk of pesticide inhalation exposure during application or post-application drift. Briefly, under the recommended application dosage applied *via* spraying using the twin-hole cone type, the calculated ADD_{inh} values of 5 % lambda-cyhalothrin EW, 20 % acetamiprid SL, and 40 % phoxim EC for applicators during pesticide spraying were 4.35×10^{-5} mg/kg·day, 5.86×10^{-6} mg/kg·day, and 1.27×10^{-7} mg/kg·day, respectively, based on the bioaccessible UE. The corresponding values of ADD_{inh} for application drift to 50 m from the agricultural fields were 8.03×10^{-9} mg/kg·day, 1.30×10^{-7} mg/kg·day, and 8.22×10^{-8} mg/kg·day for 5 % lambda-cyhalothrin EW, 20 % acetamiprid SL, and 40 % phoxim EC, respectively. In contrast, the ADD_{inh} values of 26 % lambda-cyhalothrin·acetamiprid WG and 20 % lambda-cyhalothrin·phoxim EC during pesticide spraying were estimated at 1.52×10^{-5} mg/kg·day and 1.83×10^{-5} mg/kg·day, respectively. These ADD_{inh} values were generally comparable to the values of 5 % lambda-cyhalothrin EW and significantly higher than that of 20 % acetamiprid SL and 40 % phoxim EC. For airborne pesticides measured at 50 m from the edge of the field, high ADD_{inh} values were observed within 2 h after

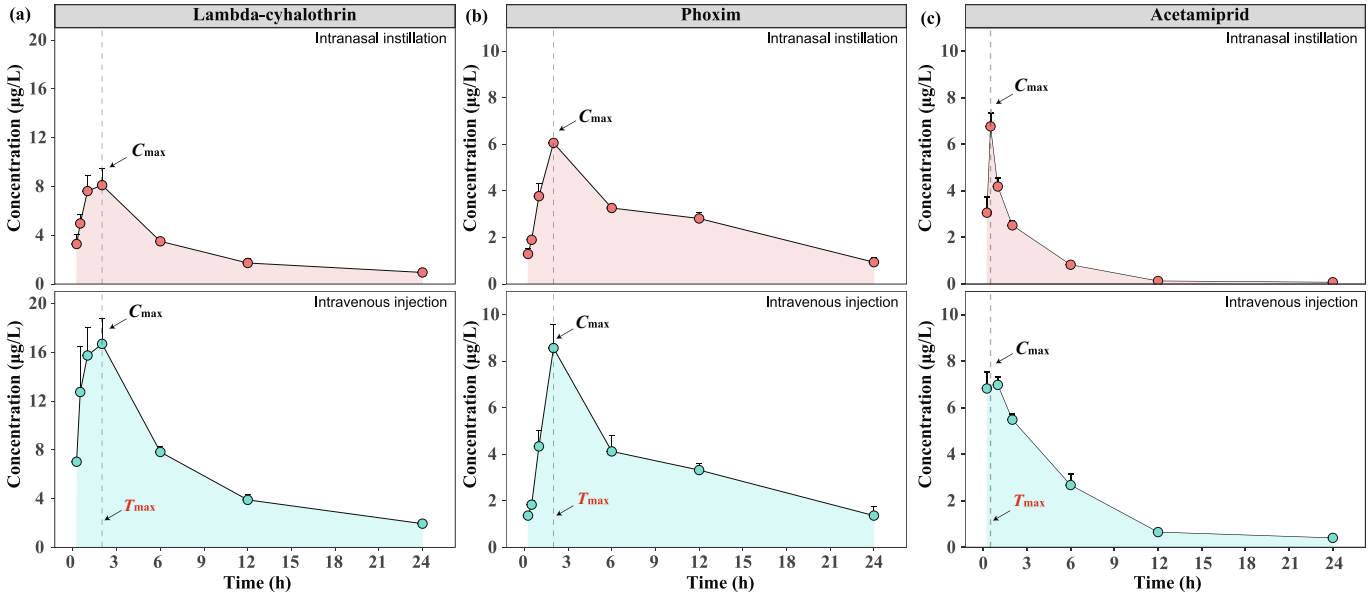

Fig. 3. Plasma concentration − time profile of lambda-cyhalothrin (a), phoxim (b), and acetamiprid (c) following intranasal instillation and intravenous exposure in mice. When a compound is detected below LOQ in the actual samples, it 1/2 LOD values are served as the concentration of pesticide residues.

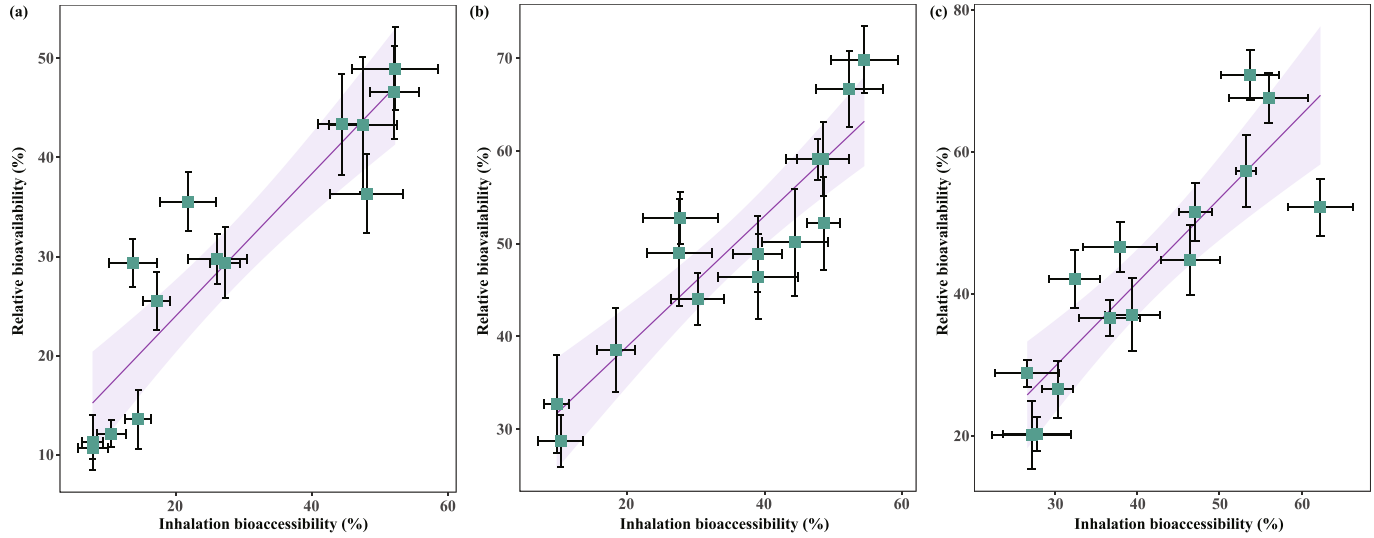

Fig. 4. The IVIVC between the inhalation bioaccessibility determined from SLF and the inhalation relative bioavailability based on a rat bioassay. The solid blue and dashed red lines represent 95 % confidence and prediction bands, respectively.

Table 1
ADD values of inhalation exposure to different formulations calculated after incorporating bioaccessibility during application or post-application.

Exposure scenarios	Formulations	Nozzles	ADD_{tota} (based on total UE, mg/kg·day)	ADD_{inh} (based on bioaccessible UE, mg/kg·day)
Applicators during application	5 % lambda-cyhalothrin EW	Single-hole	8.77×10^{-5}	4.04×10^{-5}
		Twin-hole	9.43×10^{-5}	4.35×10^{-5}
	40 % phoxim EC	Single-hole	6.75×10^{-6}	4.53×10^{-6}
		Twin-hole	7.25×10^{-6}	4.86×10^{-6}
	20 % acetamiprid SL	Single-hole	9.73×10^{-8}	4.57×10^{-8}
		Twin-hole	2.71×10^{-7}	1.27×10^{-7}
	26 % lambda-cyhalothrin·acetamiprid WG	Single-hole	3.55×10^{-5}	1.61×10^{-5}
		Twin-hole	3.35×10^{-5}	1.52×10^{-5}
	20 % lambda-cyhalothrin·phoxim EC	Single-hole	2.89×10^{-5}	1.49×10^{-5}
		Twin-hole	3.53×10^{-5}	1.83×10^{-5}
Residents at 50 m downwind from the experimental field	5 % lambda-cyhalothrin EW	Twin-hole	1.74×10^{-8}	8.03×10^{-9}
	40 % phoxim EC	Twin-hole	1.94×10^{-7}	1.30×10^{-7}
	20 % acetamiprid SL	Twin-hole	2.04×10^{-7}	8.22×10^{-8}
	26 % lambda-cyhalothrin·acetamiprid WG	Twin-hole	7.67×10^{-8}	3.18×10^{-8}
	20 % phoxim·acetamiprid EC	Twin-hole	3.48×10^{-7}	2.24×10^{-7}

application (3.18×10^{-8} mg/kg·day and 2.24×10^{-7} mg/kg·day for 20 % acetamiprid SL and 40 % phoxim EC, respectively). The results suggested that the application of mixed pesticide formulations may increase the drift risk of the active ingredients.

As a caveat, when assessing the risk of inhalation exposure based on the total UE, the calculated ADD_{total} value corresponds to 1.49–2.48 times the ADD_{inh} value obtained by incorporating inhalation bioaccessibility into the calculation. It is apparent that the total UE is a conservative estimate and represents the inhalation exposure risk in a worst-case scenario, which may lead to unnecessary concerns and costs associated with risk management. It is essential to acknowledge that this risk assessment technique is limited by the lack of specific inhalation toxicity data, warranting further investigation.

4. Conclusions

The results of this work highlight the necessity of incorporating inhalation bioaccessibility into the inhalation exposure assessment of drifting pesticides. The methodological parameters for inhalation bioaccessibility measurement were optimized using an RSM approach, which was validated by incorporating *in-vivo* data. The conservative inhalation bioaccessibility values estimated for lambda-cyhalothrin, phoxim, and acetamiprid were 46.09 %, 67.12 %, and 40.31 %, respectively. For *in-vitro* method standardization, it is important to more accurately assess the inhalation exposure risk of pesticides. Moreover, it was noted that the application of mixed pesticide formulations could increase the drift risk of the active ingredients compared to single pesticide formulations, which is of guiding significance for improving risk management practices during pesticide application. Exposure to multiple pesticide residues in combination may pose human health risks that are completely different from those presented by single exposures, warranting further investigation of the combined exposure risk of the active ingredients from mixed pesticide formulations. Collectively, our findings contribute insights into the assessment of pesticide inhalation exposure based on bioaccessibility and provide guidance for the safe application of pesticides.

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CRediT authorship contribution statement

Ke Fang: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Funding acquisition, Formal analysis, Data curation. **Tingting Li:** Methodology, Investigation, Formal analysis. **Weizhang Qi:** Methodology, Investigation, Formal analysis. **Li Zhang:** Validation, Supervision, Software, Formal analysis. **Yingmei Hu:** Software, Methodology. **Yuying Liu:** Methodology, Investigation. **Yanhong Shi:** Visualization, Validation, Supervision, Software. **Haiqun Cao:** Visualization, Validation, Supervision. **Jinjing Xiao:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.177254.

Data availability

Data will be made available on request.

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