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A lognormal model for evaluating maximum residue levels of pesticides in crops *

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To evaluate pesticide regulatory standards in agricultural crops, we introduced a regulatory modeling framework that can ...exibly evaluate a population's aggregate exposure risk via maximum residue levels (MRLs) under good agricultural practice (GAP). Based on the structure of the aggregate exposure model and the nature of variable distributions, we optimized the framework to achieve a simpli...ed mathe- matical expression based on lognormal variables including the lognormal sum approximation and lognormal product theorem. The proposed model was validated using Monte Carlo simulation, which demonstrates a good match for both head and tail ends of the distribution (e.g., the maximum error ¼ 2.01% at the 99th percentile). In comparison with the point estimate approach (i.e., theoretical maximum daily intake, TMDI), the proposed model produced higher simulated daily intake (SDI) values based on empirical and precautionary assumptions. For example, the values at the 75th percentile of the SDI distributions simulated from the European Union (EU) MRLs of 13 common pesticides in 12 common crops were equal to the estimated TMDI values, and the SDI values at the 99th percentile were over 1.6- times the corresponding TMDI values. Furthermore, the model was re...ned by incorporating the lognormal distributions of biometric variables (i.e., food intake rate, processing factor, and body weight) and varying the unit-to-unit variability factor (VF) of the pesticide residues in crops. This ensures that our proposed model is ...exible across a broad spectrum of pesticide residues. Overall, our results show that the SDI is signi...cantly reduced, which may better re...ect reality. In addition, using a point estimate or lognormal PF distribution is effective as risk assessments typically focus on the upper end of the distribution.

1. Introduction

Pesticides have been designed and synthesized to eradicate or inhibit pests, weeds, and diseases, and are widely applied to croplands to increase production worldwide. Globally, over 5.9 million tons of pesticides were applied for agricultural purposes in 2018 (FAO, 2018). After application, a large portion of pesticides remains on or enters crop tissues via direct absorption and root uptake, which can result in serious health risks for livestock and humans (Barron et al., 2017; Diop et al., 2016; Erlacher and Wang, 2011; Fantke et al., 2011; García-Gal an et al., 2020; Hlihor et al., 2019; Hwang et al., 2018).

To protect population health, international agencies regulate pesticide maximum residue levels (MRLs), which are legal limits that must not be exceeded (Brancato et al., 2018; Li, 2018a; Li and Jennings, 2017; MacLachlan and Hamilton, 2010; Wilson and Otsuki, 2004). Pesticide MRLs are regulated for hundreds of agri- cultural commodities including fruits, vegetables, grains, seeds, meat, dairy products, and animal feeds. Worldwide, at least 114 countries have set pesticide MRLs for these products, and cluster analysis indicates that most countries have adopted the standards of the European Union (EU) and Codex Alimentarius (or Codex) (Li, 2018b). In general, the regulatory process of pesticide MRLs in- tegrates good agricultural practice (GAP), pesticide application patterns, market residue monitoring, public health, and economic/ trade compliance (Handford et al., 2015; MacLachlan and Hamilton, 2010). From a regulatory perspective, the worst-case MRL scenario is always applied to protect population health.

As human exposure to pesticides via the ingestion of

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agricultural crops should be assessed cumulatively, Li (2018a, b) evaluated the effectiveness of worldwide MRLs on population health by calculating the aggregate theoretical maximum dose intake (TMDI), which applies a point-estimation method using MRLs as the hypothetical levels of pesticide residues in crops. Although Li (2018a, b) study provided a simpli...ed evaluation method for MRLs, the aggregate exposure risks calculated via the TMDI are largely theoretical rather than re...ecting real situations. Estimates might be too conservative, for example, to practically regulate due to the lack of lifecycle analysis, such as emission patterns and food processing effects, especially for pesticide applications under GAP. Therefore, the aggregate TMDI proposed by Li (2018a, b) could overestimate population health risks. If such a conservative approach is applied for the regulatory process, some MRLs will need be revised to offset the overestimated TMDI, which is impractical and unnecessary because the level of a pesticide typically follows a right-skewed lognormal distribution, and a MRL is always located at the higher end of the distribution. On the other hand, some investigations of market data show that some crop samples have pesticide residues above the legal limits, indicating that the TMDI approach can sometimes underestimate exposure risks.

To address these challenges, this study aims to develop a backward model that can more realistically simulate pesticide residue levels in crops to characterize population-scale aggregate exposure risk. First, we introduced a regulatory modeling framework, enhanced by the lognormal sum approximation, to simulate a population's aggregate exposure to multiple agricultural crops, which could evaluate current MRLs more accurately and practically. Then, we ...xed human biometric variables focusing on the evaluation of existing MRLs in common crops, such that a general model was applied based only on the distributions of the back-simulated residue levels in crops. Furthermore, we re...ned and improved the model by coupling the lognormal product theorem to optimize a population's theoretical exposure by varying the input variables and adding a food-processing factor. In doing so, our lognormal-operation-based regulatory modeling framework provided a more practical tool for regulatory agencies to assess theoretical aggregate exposure risks and optimize the MRL regulatory process.

2. Methods

2.1. Modeling framework

Fig. 1 shows a conceptual diagram of the lognormal-operation-based regulatory modeling framework, which includes the following four steps: 1) the collection of MRLs of pesticide residues in crops; 2) the backward estimation of pesticide residue levels in crops; 3) an aggregate health risk (chronic) assessment of pesticides via the ingestion of crops; and 4) model re...nement and improvement. Using this framework, we attempted to backward estimate the distributions of pesticide residue levels in crops assuming lognormal distributions due to their widespread application and ...eld observations. Furthermore, we assessed aggregate health risks according to the estimated residue levels to evaluate current MRLs based on the arithmetic operations of lognormal variables. These operations included the lognormal production theorem and lognormal sum approximations, which we combined here as a useful tool for predicting risk and regulating MRLs when lognormal variables need to be summed or multiplied. It must be noted that some crop pesticide MRLs were set at their default values due to a lack of available ...eld trials, although the MRL-based distributions could still be back simulated by varying the distribution parameters.

2.2. Backward residue estimates

As lognormal distributions are widely applied to describe the distributions of residue levels in crops and many studies have shown that lognormal distributions provide a good ...t, the backward estimation of residue levels was based on the lognormal distribution of residue levels. Thus, the simulated level of a pesticide residue in crop i (C_i, mg kg^{-1}) follows the lognormal distribution $C_i \sim LN(m_{C,i}, s^2_{C,i})$, where $m_{C,i}$ and $s_{C,i}$ are the average and standard deviation of the natural logarithms of C_i, respectively. If the unit-to-unit variability factor (VF) of the pesticide residue in crops is de...ned as the ratio of the residue level at the 97.5th percentile of the distribution to the average value, the following can be established:

$$VF_R = \frac{\exp(m_{C,i} + 1.96\, s_{C,i})}{\exp(m_{C,i} + 0.5\, s^2_{C,i})} = \exp(1.96\, s_{C,i} - 0.5\, s^2_{C,i}) \quad (1a)$$

$$P_R(C_i) = F\left(\frac{\ln(MRL_i) - m_{C,i}}{s_{C,i}}\right) \quad (1b)$$

where VF_R is the unit-to-unit variability factor used in the regulatory process, which can be directly obtained from ...eld trials for crop i. Here, a default value of 2.0 was applied for VF_R to simplify the regulatory calculation based on chronic health risk management. It should be noted that VF can vary for different pesticides in different crops, and if an acute risk assessment is conducted, VF should be set much higher than 2.0; $P_R(C_i)$ is the probability of C_i MRL_i, i.e., a cumulative probability where the subscript R indicates that the cumulative probability meets regulatory requirements and $F(\cdot)$ is the cumulative distribution function (CDF) of a standard normal distribution. If MRL_i is obtained from ...eld trials under GAP, a relatively safe and balanced value can be

Fig. 1. Conceptual diagram of the lognormal-operation-based modeling framework used to evaluate maximum residue levels (MRLs) of pesticide.

established from the distribution of C_i, i.e., at the higher end of the distribution, considering both population health risks and agricultural productivities. Here, we assumed MRL_i was the 97.5th percentile of the distribution of C_i, i.e., MRL_i is higher than 97.5% of C_i, and $P_R(C_i)$ in Eq. (1b) is equal to 97.5%, which approximates most observations. For example, pesticide residues in approximately 2% of United States (US) domestic vegetable samples exceed their respective MRLs; between 2011 and 2013, approximately 4e5% of fruits and vegetables consumed in Thailand exceeded the corresponding MRLs; the EU Coordinated Control Programme (EUCP) and the EU Coordinated and National Programme (EUNP) reported that levels of pesticide residues fell below MRLs in 98.3% and 96.2% of tested samples, respectively, where 2.2% of the samples exceeded legal limits; and the EUNP previously reported that 97.2% of samples were within the established MRLs (EFSA, 2018; Wanwimolruk et al., 2015). Therefore, $m_{C,i}$ and $s_{C,i}$ can be back-calculated in Eqs. (1a) and (1b) based on the approximated position of MRLs in the C distributions and using a default regulatory value of VF$_R$.

2.3. Aggregate health risk assessment

The aggregate health risk assessment of a pesticide was conducted by simulating the corresponding exposure dose through ingestion of multiple pesticide-contaminated crops, which was further compared to the acceptable daily intake (ADI, mg kg^{-1} d^{-1}), which is the recommended daily intake dose over a lifetime without developing considerable adverse health effects. Thus, the simulated daily intake of a pesticide through selected agricultural commodities (SDI, mg kg^{-1} d^{-1}) can be expressed as follows:

$$SDI = \frac{1}{BW}\sum_{i=1}^{n}(IR_i C_i) \quad (2)$$

where BW (kg) is the human body weight of adults, and IR_i (kg d^{-1}) is the intake rate of crop i. If a point estimate for IR_i is used, then $IR_i C_i \sim LN(m_{C,i} + \ln(IR_i), s^2_{C,i})$. We did not find any closed forms of probability density functions (PDFs) or moment generating functions (MGFs) for the sum of independent variables, but this was not the case for the identical lognormal random variables. According to Mehta et al. (2007), a lognormal variable can still be applied to approximate the sum of lognormal variables, i.e., $T \sim LN(m_T, s^2_T)$, where $T = \sum_{i=1}^{n}(IR_i C_i)$ and m_T and s_T are the mean and standard deviation of the natural logarithm of the variables, respectively. To calculate m_T and s_T, the MGF of T was applied as follows:

$$\hat{J}_T(s) = \int_0^{\infty} \exp(-st) f(t)\,dt = \int_0^{\infty} \exp\left(-e^{t} \cdot \exp\left(\frac{(\ln t - m_T)^2}{2 s^2_T}\right)\right) dt \quad (3)$$

where $\hat{J}_T(s)$ and $f(t)$ are the MGF and the PDF of T, respectively. Due to the unavailability of the closed-form of $\hat{J}_T(s)$, the Gauss-Hermite integration was applied to expend Eq. (3) (Liu, 2003; Mehta et al., 2007) as weighted integrals, thus:

$$\hat{J}_T(s) = \sum_{k=1}^{K} w_k \cdot \exp\left(-\exp\left(\sqrt{2}\, a_k s_T + m_T\right)\right) + R_K \quad (4)$$

where w_k and a_k are the weight and abscissa, respectively, which can be found in Abramowitz and Stegun (1970) when $K = 20$. R_K is the reminder term, and by defining the Gauss-Hermite-based MGF (i.e., $\hat{J}_T(s)$) (Mehta et al., 2007), R_K is removed as follows:

$$\hat{J}_T(s) = \sum_{k=1}^{K} w_k \cdot \exp\left(-\exp\left(\sqrt{2}\, a_k s_T + m_T\right)\right) \quad (5)$$

As $IR_1C_1; \ldots; IR_nC_n$ are independent random variables, the MGF of $\sum_{i=1}^{n}(IR_i C_i)$ can be expressed as follows:

$$\hat{J}_T(s) = \prod_{1}^{n} \hat{J}_{IR_i C_i}(s) \quad (6)$$

then, $\hat{J}_T(s)$ can also be expressed as the product of the Gauss-Hermite-based individual MGF, i.e., $\prod_{1}^{n} \hat{J}_{IR_i C_i}(s)$. Therefore, m_T and s_T can be derived by selecting two different s values, thus:

$$\sum_{k=1}^{K} w_k \cdot \exp\left(-\exp\left(\sqrt{2}\, a_k s_T + m_T\right)\right) = \prod_{1}^{n} \hat{J}_{IR_i C_i}(s_1) \quad (7a)$$

$$\sum_{k=1}^{K} w_k \cdot \exp\left(-\exp\left(\sqrt{2}\, a_k s_T + m_T\right)\right) = \prod_{1}^{n} \hat{J}_{IR_i C_i}(s_2) \quad (7b)$$

We solved m_T and s_T using the 'fsolve' package in MATLAB. If a point estimate of BW is applied, then SDI follows a lognormal distribution, where $SDI \sim LN(m_T - \ln(BW), s^2_T)$. Then, the probability of SDI < ADI for a pesticide, i.e., the population is suitably protected by current crop MRLs, can be expressed as follows:

$$P_R(SDI) = F\left(\frac{\ln(ADI) - (m_T - \ln(BW))}{s_T}\right) \quad (8)$$

where the subscript R denotes the regulatory process, indicating that the aggregate health risks are estimated based on current regulations under GPA. Thus, $P_R(SDI)$ was applied as a robust indicator to help evaluate current pesticide MRLs in various crops.

2.4. Data collection

To evaluate the regulatory performance of current pesticide residue standards in crops, we selected MRLs from the relevant EU and Codex datasets, which are widely applied worldwide to regulate pesticides in agricultural commodities. For IR_i, we used data collected by Li (2018a, b) and calculated averages for EU member states and other worldwide countries and territories. For BW, a default value of 70 kg was used in Eq. (8) (Schwab et al., 2005). As hundreds of different types of fruits and vegetables are consumed worldwide, some of which are not widely consumed, we selected the most commonly consumed foods from four major categories, specifically grain crops (i.e., corn, rice, and wheat), vegetables (i.e., onions, potatoes, and tomatoes), fruits (i.e., apples, bananas, grapes, and oranges), and drinks (i.e., coffee beans and tea leaves) (Li, 2018b). It must be noted that local investigations to derive IR_i and BW values for populations should be conducted if risk assessors wish to focus on population health risks at the city level.

3. Results and discussion

3.1. Model validations

We selected glyphosate and chlorpyrifos as examples to illustrate the modeling process, which are two of the most commonly used pesticides worldwide that are frequently detected in agricultural crops (Dar et al., 2019; Henault-Ethier et al., 2017; Singh et al., 2020). In addition, glyphosate and chlorpyrifos are broad-spectrum

pesticides used to treat a range of crops (Benbrook, 2016; Deb and Das, 2013; Duke and Powles, 2008), thereby increasing their aggregate exposure risks. For example, chlorpyrifos has been widely detected in all kinds of vegetables, fruits, and agricultural meat products (Ferr e et al., 2018; Juraske et al., 2011; Li, 2020a). The MRLs for glyphosate and chlorpyrifos from the EU and Codex standards (European Commission, 2020; FAO/WHO, 2019) and their backward estimates of the lognormal parameters are listed in Table 1. To solve the unknown variables m_T and s_T in Eqs. (7a) and (7b), we set $s_1 = 1.0$ and $s_2 = 0.2$, as recommended by Mehta et al. (2007); s_1 and s_2 are two positive values that can be arbitrarily selected to adjust the mismatch between the proposed model (i.e., the sum of lognormal variables) and the original simulation. Increasing or decreasing s_1 and s_2 can affect the accuracy of the proposed model at the higher or lower end of the distribution, which can be used to ...nd the ideal proposed model by integrating the complementary CDF (CCDF), after which the portion of the distribution is determined. The proposed models of the sum of lognormal variables for four situations are illustrated in Fig. 2. This shows the distributions of m_T and s_T for $\sum_{i=1}^{n}(IR_i C_i)$ (10^6 iterations) of the aggregate theoretical intake of glyphosate and chlorpyrifos back−calculated from the EU and Codex MRLs in 12 selected agri−cultural commodities. These were compared with standard Monte Carlo simulation, i.e., the distributions generated by simulating and summing the individual $IR_i C_i$. The results indicated that the pro−posed models provide a good match with the Monte Carlo simu−lations for both low and high ends of the distributions.

The parameters m_T and s_T obtained from Eqs. (7a) and (7b) for the EU MRLs of glyphosate are 0.796 and 0.363, respectively, based on which the 95th and 99th percentiles of the proposed distribu−tion are 4.02 mg d^{-1} and 5.15 mg d^{-1}, respectively. The 95th and 99th percentiles obtained from the regular Monte Carlo simulation for the EU MRLs of glyphosate are 4.05 mg d^{-1} and 5.24 mg d^{-1}, respectively, which are very close to the results from our model. More validation results are listed in Table 2, which show that the largest error between these two methods is 2.01%, which is acceptable for theoretical risk estimates. Such consistency dem−onstrates the feasibility of the proposed model based on a single set of parameters (i.e., m_T and s_T) for lognormal sum approximation. From the calculated errors, the values at the head and tail ends of the distributions of the two models have larger differences than in the center of the distribution, which can be re...ned by adjusting s_1 and s_2.

Fig. 2. Proposed model using lognormal sum approximation ($x = \sum_{i=1}^{n}(IR_i C_i)$, mg d^{-1}) plotted as cumulative distribution functions (CDF, F(x)) compared to Monte Carlo simulation outputs (10^6 iterations). #1: EU MRLs of glyphosate; #2: EU MRLs of chlorpyrifos; #3: Codex MRLs of glyphosate; #4: Codex MRLs of chlorpyrifos.

3.2. Health risk implications

To better protect population health, we applied the proposed model to back−calculate the aggregate exposure to pesticide resi−dues from current MRLs, and compared the results with both ADI and TMDI values from previous studies. A total of 13 pesticides were selected (Table 3) based on their widespread use and frequent detection (Li, 2018b). It is noted that some of the MRLs collected by Li (2018a, b) are considered out−of−date and the original sources are no longer valid (formerly the "Global MRL Database"). In these cases, we used the MRLs from the EU and Codex (European Commission, 2020; FAO/WHO, 2019) and re−calculated the TMDI values using Li (2018a, b) point−estimate approach. Table 3 lists the TMDI values, the SDI values at the 50th, 95th, and 99th percentiles of the proposed lognormal distribution, and the $P_R(SDI)$ values calculated based on Eq. (8). The EU regulates all of the selected 13 pesticides in 12 common crops. Codex does not regulate any MRLs for atrazine, diuron, metolachlor, and tri...uralin for the selected crops, such that the simulated results are not applicable for these four pesticides. Where a pesticide is not regulated for a crop, we assumed the back−estimated level was zero. For example, Codex promulgates chlorpyrifos MRLs for nine of the 12 selected crops, meaning the proposed model back−calculated the distributions of chlorpyrifos in nine crops for Codex.

Table 1
Summary of MRLs of glyphosate and chlorpyrifos promulgated by the EU and Codex, and IR estimated for EU member states and other worldwide countries.

	Apple	Banana	Coffee bean	Corn/Maize	Grape	Onion	Orange	Potato	Rice	Tea	Tomato	Wheat
Glyphosate												
EU MRL (mg kg^{-1})	0.1	0.1	0.1	1	0.5	0.1	0.5	0.5	0.1	2	0.1	10
m_C	2.63	2.63	2.63	0.33	1.02	2.63	1.02	1.02	2.63	0.37	2.63	1.98
Codex MRL (mg kg^{-1})	e	0.05	e	5	e	e	e	e	e	e	e	30
m_C	e	3.32	e	1.28	e	e	e	e	e	e	e	3.08
Chlorpyrifos												
EU MRL (mg kg^{-1})	0.01	4	0.1	0.05	0.01	0.2	1.5	0.01	0.5	2	0.1	0.5
m_C	4.93	1.06	2.63	3.32	4.93	1.94	0.08	4.93	1.02	0.37	2.63	1.02
Codex MRL (mg kg^{-1})	e	2	0.05	0.05	0.5	0.2	e	2	0.5	2	e	0.5
m_C	e	0.37	3.32	3.32	1.02	1.94	e	0.37	1.02	0.37	e	1.02
IR (kg d^{-1})												
EU member states	4.88E−02	2.15E−02	1.70E−02	2.57E−02	2.49E−02	2.45E−02	8.49E−02	1.84E−01	1.23E−02	1.24E−03	6.40E−02	2.83E−01
Other worldwide countries	2.74E−02	3.61E−02	6.33E−03	6.77E−02	1.18E−02	2.67E−02	4.83E−02	9.11E−02	9.62E−02	2.70E−03	5.29E−02	1.86E−01

— denotes unavailable information.
s_C for glyphosate and chlorpyrifos in the chosen common crops was estimated as 0.39 using a VF of 2.0.

Table 2
Comparison of simulated $\sum_{i=1}^{n}(IR_i \times C_i)$ values between the lognormal sum approximation (proposed model) and Monte Carlo simulation (10^6 iterations).

Method	Percentile	$\sum_{i=1}^{n}(IR_i \times C_i)$ (mg d^{-1}) simulated from EU MRLs		$\sum_{i=1}^{n}(IR_i \times C_i)$ (mg d^{-1}) simulated from Codex MRLs	
		Glyphosate	Chlorpyrifos	Glyphosate	Chlorpyrifos
Lognormal sum approximation (proposed model)	5th	1.22	0.20	2.38	0.22
	25th	1.74	0.25	3.39	0.27
	50th	2.22	0.29	4.34	0.32
	75th	2.83	0.34	5.54	0.37
	95th	4.02	0.41	7.89	0.45
	99th	5.15	0.48	10.11	0.52
Monte Carlo simulation	5th	1.23	0.20	2.39	0.23
	25th	1.73	0.25	3.38	0.27
	50th	2.21	0.29	4.32	0.32
	75th	2.82	0.33	5.54	0.36
	95th	4.05	0.42	7.97	0.45
	99th	5.24	0.49	10.31	0.53
Error between lognormal sum approximation and Monte Carlo simulation	5th	0.77%	0.83%	0.32%	1.44%
	25th	0.34%	0.05%	0.42%	0.09%
	50th	0.48%	0.21%	0.35%	0.43%
	75th	0.18%	0.25%	0.09%	0.51%
	95th	0.67%	0.17%	0.98%	0.35%
	99th	1.65%	0.87%	2.01%	1.75%

Note: The error between the lognormal sum approximation and Monte Carlo simulation is de...ned as the absolute difference of the simulated results between the two methods divided by the result from the Monte Carlo simulation.

Table 3
Comparison of the daily intake (SDI, mg kg^{-1} d^{-1}) of 13 pesticides in commonly consumed crops simulated by the proposed model and theoretical maximum daily intake (TMDI, mg kg^{-1} d^{-1}) based on the point estimate approach.

Pesticide	CAS No.	ADI (mg kg^{-1} d^{-1})	EU MRLs					Codex MRLs				
			TMDI (mg kg^{-1} d^{-1})	SDI (mg kg^{-1} d^{-1}) Lognormal sum approximation				TMDI (mg kg^{-1} d^{-1})	SDI (mg kg^{-1} d^{-1}) Lognormal sum approximation			
				50th	75th	99th	P_R(SDI)		50th	75th	99th	P_R(SDI)
2,4−D	94−75−7	1.00E−02	1.00E−02	7.46E−03	9.26E−03	1.57E−02	82.1%	5.77E−03	4.22E−03	5.39E−03	9.79E−03	99.6%
Atrazine	1912−24−9	1.00E−03	5.79E−04	4.44E−04	5.06E−04	6.96E−04	100.0%	e	e	e	e	e
Chlorothalonil	1897−45−6	1.50E−02	1.30E−02	1.02E−02	1.18E−02	1.71E−02	96.0%	1.26E−02	9.44E−03	1.13E−02	1.77E−02	98.2%
Chlorpyrifos	2921−88−2	1.00E−03	5.44E−03	4.13E−03	4.79E−03	6.89E−03	0.0%	5.95E−03	4.52E−03	5.23E−03	7.44E−03	0.0%
Diazinon	333−41−5	7.00E−04	1.38E−04	1.01E−04	1.29E−04	2.30E−04	100.0%	4.29E−04	1.82E−04	3.89E−04	2.50E−03	100.0%
Dicamba	1918−00−9	3.00E−02	8.70E−03	6.37E−03	8.14E−03	1.48E−02	100.0%	5.34E−03	3.86E−03	5.02E−03	9.56E−03	100.0%
Diuron	330−54−1	2.00E−03	1.24E−04	9.02E−05	1.17E−04	2.21E−04	100.0%	e	e	e	e	e
Glyphosate	1071−83−6	1.00E−01	4.32E−02	3.17E−02	4.04E−02	7.36E−02	99.9%	8.48E−02	6.19E−02	7.92E−02	1.44E−01	90.7%
Malathion	121−75−5	2.00E−02	3.93E−02	2.90E−02	3.60E−02	6.10E−02	12.5%	2.85E−02	1.21E−02	1.53E−02	2.71E−02	94.2%
Mancozeb	8018−01−7	3.00E−02	1.99E−02	1.53E−02	1.72E−02	2.30E−02	100.0%	7.98E−03	6.11E−03	6.91E−03	9.34E−03	100.0%
MCPA	94−74−6	5.00E−04	1.19E−03	8.87E−04	1.07E−03	1.69E−03	2.0%	5.42E−04	3.94E−04	5.12E−04	9.73E−04	80.6%
Metolachlor	87392−12−9	1.50E−01	5.66E−04	4.31E−04	5.03E−04	7.35E−04	100.0%	e	e	e	e	e
Tri...uralin	1582−09−8	7.50E−03	1.24E−04	9.02E−05	1.17E−04	2.21E−04	100.0%	e	e	e	e	e

— indicates that a MRL is not set by Codex; ADI values may vary from different sources.

The simulated $P_R(SDI)$ values from the EU regulations indicate that nine of the 12 pesticides are regulated at relatively safe MRLs (i.e., $P_R(SDI) > 95\%$). The calculated $P_R(SDI)$ values for chlorpyrifos and MCPA are extremely low (0.0% and 2.0%, respectively), indicating that their corresponding ADI values are at the lower end of the SDI distributions. Surprisingly, the TMDLs of the 13 pesticides calculated from the EU MRLs, which are considered to be extremely conservative, approximately match the values at the 75th percentile of the SDI distributions (Fig. 3) and are approximately equal to 0.6-times the SDI values at the 99th percentile. This is because we empirically applied the MRL as the value at the 97.5th percentile of the level distribution and used a VF of 2.0 for the selected pesticides in common crops. For the EU MRLs, these preliminary results indicate that the risks simulated by the proposed model under empirical assumptions are higher than those based on the conservative TMDI approach. For the Codex MRLs, the $P_R(SDI)$ values for most of the pesticides are above 90% because MRLs are not set for some crops. It is noted that we only simulated the aggregate exposure for the selected crops, and if an allocation factor is

Fig. 3. Simulated daily intake (SDI) plotted against the theoretical maximum daily intake (TMDI) for EU MRLs.

considered for other crops and other oral exposure routes, greater health risks will be induced based on current MRLs. Therefore, our proposed model suggests that current MRLs may result in a greater degree of population–level health risks than previously thought.

3.3. Model re...nement, improvement, and limitations

As shown by many risk studies, lognormal distributions can provide a good ...t of population intake rates of crops and other agricultural commodities (Hosseini Koupaie and Eskicioglu, 2015; Mu ñoz–Pradas, 2011; Ruf...e et al., 1994; Spliethoff et al., 2016). Therefore, IR_i for a population follows a lognormal distribution with logarithm parameters $m_{IR;i}$ and $s_{IR;i}$. According to the lognormal product theorem, the product of independent variables IR_i and C_i follows a lognormal distribution, with the parameters $m_{IR;i} + m_{C;i}$ and $\sqrt{s^2_{IR;i} + s^2_{C;i}}$, i.e., $IR_i C_i \sim LN(m_{IR;i} + m_{C;i}, \sqrt{s^2_{IR;i} + s^2_{C;i}})$ (Li, 2020b). Therefore, $\sum_{i=1}^{n} (IR_i C_i)$ in Eq. (2) can be solved using lognormal sum approximation. In Eq. (2), $\frac{1}{BW}$ is not within the summation term because each simulated result of SDI denotes the exposure dose of a pesticide for an individual, and variations in BW for individuals (e.g., of different ages or with different health conditions) were not considered here. A lognormal distribution can also be assumed for BW, as adopted in other studies (Burmaster and Hull, 1997; Gualandi and Toscani, 2019; Smith, 1994), and the lognormal product theorem can again be applied to the product of $\frac{1}{BW}$ and $\sum_{i=1}^{n} (IR_i C_i)$. Therefore, SDI follows a lognormal distribution as $SDI \sim LN(m_T - m_{BW}, \sqrt{s^2_T + s^2_{BW}})$, where $m_{BW} = 4.15$ and $s_{BW} = 0.2$ are estimated as the mean and standard deviation of the logarithm of BW, respectively. Based on this, the probability that SDI ≤ ADI for a pesticide, i.e., the population is adequately protected by the current MRLs of crops, can be expressed as follows:

$$P_R(SDI) = F\left(\frac{\ln(ADI) - (m_T - m_{BW})}{\sqrt{s^2_T + s^2_{BW}}}\right) \quad (9)$$

To illustrate the model after re...nement using the lognormal product theorem, we estimated $s_{IR;i}$ by assuming a con...dence factor (CF) of 3 (i.e., $0.5 \ln(CF)$), indicating that 95% of the IR_i values fall in $\frac{1}{3}\exp(m_{IR;i}) : 3\exp(m_{IR;i})$ (MacLeod et al., 2002). We then calculated the $m_{IR;i}$ values using $s_{IR;i}$ and the arithmetic averages (i.e., IR_i in Table 1).

Fig. 4 illustrates the resulting distributions of $\frac{1}{BW}\sum_{i=1}^{n} (IR_i C_i)$ for the EU MRLs of chlorpyrifos and glyphosate compared to the previously proposed distributions based on the point estimates of IR_i and $\frac{1}{BW}$. The results indicate that the re...ned distributions yield lower SDIs, with values at the 99th percentile of the SDI distribution of 2.04×10^{-3} mg kg^{-1} d^{-1} and 3.79×10^{-3} mg kg^{-1} d^{-1} for chlorpyrifos and glyphosate, respectively. These values are lower than the simulated results shown in Table 3. Furthermore, the $P_R(SDI)$ value of chlorpyrifos calculated according to Eq. (9) is 86.3%, which is much higher than the previously estimated $P_R(SDI)$ value (i.e., 0.0%) shown in Table 3. This indicates that coupling the lognormal sum approximation with the lognormal product theorem can better re...ect real–life exposure scenarios, and the overestimation of theoretical health risks based on current MRLs could, therefore, be avoided.

Pesticide MRLs in foods are not always based on risk data but can be set according to detection limits or generic uncertainty factors for particular residues. For example, the EU MRLs of chlorpyrifos in apples, grapes, and potatoes are 0.01 mg kg^{-1}, which is a default value when ...eld data or other information are not available. In these cases, the backward estimation of residue levels based on Eqs. (1a) and (1b) should be adjusted to better re...ect the true situation. In this regard, we varied VF_R in Eq. (1a) to further evaluate current MRLs. For example, Fig. 5 shows the CDFs of SDI for the EU glyphosate MRL using this approach. The results indicate that varying VF_R can signi...cantly affect the estimated values at the lower end of the distribution but has far less impact on values at the higher end (e.g., at the 95th percentile). This is because $P_R(C_i)$ is kept constant in Eq. (1b) (i.e., at 97.5%) as a soft cap on the market residue levels. Furthermore, the right–skew of the lognormal distribution and the changing shape and location parameters with the constant 97.5th percentile signi...cantly affects the head values.

In addition, $P_R(C_i)$ in Eq. (1b) may not match the 97.5th percentile of the distribution exactly, especially when GAP is not followed. In this regard, $P_R(C_i)$ values can be varied to better re...ect reality. However, from a regulatory perspective, the 97.5th percentile of the distribution should be the bottom line $P_R(C_i)$ to establish MRLs and monitor residue levels, otherwise populations

Fig. 4. Simulated daily intake (SDI, mg kg^{-1} d^{-1}) for the EU MRLs using lognormal distributions for IR and BW (plot #2 for chlorpyrifos and plot #4 for glyphosate) plotted as cumulative distribution functions versus SDI using point estimates for IR and BW (plot #1 for chlorpyrifos and plot #3 for glyphosate).

Fig. 5. Simulated daily intake (SDI, mg kg^{-1} d^{-1}) of glyphosate based on the lognormal sum and product methods for the EU MRLs plotted as cumulative distribution functions by varying the unit–to–unit variability factors (VFs).

may be exposed to pesticide levels that exceed the reference health dose.

As a further consideration, before consumption, agricultural crops undergo harvest, storage, transportation, industrial processing, and cooking, such that the impact of food-processing factors on the pesticide residues in crops should be considered (Fantke et al., 2012). While the precautionary approach is a good starting point from a regulatory perspective, especially when exposure or toxicological information is limited, overestimated risk could be cumulative in aggregate exposure assessments. Indeed, while pesticide concentrations in crops are typically reduced as a result of food processing, this is not always the case. For example, oranges processed for juice and drying go through several steps including washing, peeling, concentrating, and filtering, which affects the distribution of pesticide residues in the resulting products (Li et al., 2012). Furthermore, customers may purchase non-local crops grown where the uptake of pesticides is different as a function of the weather and other geographic conditions (Li, 2020c).

To address this, we further modified our model by inserting the processing factor (PF_i), which enforced positive values of crop i in Eq. (2), such that $PF_i IR_i C_i \sim LN(m_{C,i} + \ln(PF_i IR_i), s^2_{C,i})$ if a point estimate of PF_i and IR_i is applied. Again, to estimate population exposure risks, a distribution can best represent the real situation, and if a lognormal distribution of PF_i (i.e., $PF_i \sim LN(m_{PF,i}, s^2_{PF,i})$) is applied (van der Voet et al., 2009), then $PF_i IR_i C_i \sim LN(m_{IR,i} + m_{C,i} + m_{PF,i}, s^2_{IR,i} + s^2_{C,i} + s^2_{PF,i})$ according to the lognormal product theorem (Li, 2020b). PF_i should differ between different crops; however, to illustrate the application of the improved model, we applied a point estimate with a value of 0.3 and a lognormal PF distribution for chlorpyrifos in all the selected crops. m_{PF} and s_{PF} in the lognormal PF distribution were estimated from the arithmetic average of 0.3 and a CF value of 3.0 (i.e., 95% of the values fall within 1/3- and 3.0-times the median). Based on the lognormal operation, we generated parameters for the lognormal distribution of $\sum_{i=1}^{n}(PF_i IR_i C_i)$ using a point estimate and a lognormal PF distribution, respectively. A lognormal BW distribution was then incorporated, i.e., $BW \sim LN(m_{BW} = 4.15, s^2_{BW} = 0.04)$, giving the lognormal distributions of the SDI of chlorpyrifos and glyphosate based on the EU MRLs (Fig. 6).

The results indicate that incorporating the PF for both point estimates and lognormal distributions can significantly reduce the corresponding SDI values. Furthermore, using a lognormal distribution for PF reduces the difference between the SDI as determined from the point estimate at the upper end of the distribution more so than at the lower end. As the upper end of the distribution is of most value for risk assessment, our proposed model suggests that a point estimate of PF (equal to the arithmetic average of the values in a lognormal distribution) should be sufficient for refining the model.

Through our proposed model, simple lognormal distributions of SDI can be generated for different situations, which indicate that some pesticide MRLs in crops are regulated below the limit of detection (LOD) and limit of quantification (LOQ). As such, obtaining field data to confirm the validity of key variables, such as VF and $P_R(C_i)$, is challenging. In this regard, we suggest that Bayesian inference for left-censored data (Chen et al., 2013) or lifecycle modeling (Fantke et al., 2011) could be incorporated in future studies to better explore the possible quantitative relationships between MRLs and real-life residue levels.

It is noted that although the assumption of independence between different crops is reasonable and justifiable for a population-level assessment, for individuals, it is more logical to conduct calendar-based studies because intake rates of different crops might be correlated due to personal choice. Thus, for individual risk assessment, new mathematical approaches that focus on the dependent lognormal variables should be developed. Muhammad et al. (2018) developed a non-parametric method to predict individual food consumption risk, which offers an alternative to using lognormal variables. In addition, our simulations based on estimated distributions of human biometric variables represent initial estimates only and, therefore, provide an approximate picture of overall food consumption risk. Where risk assessment or regulatory standards are needed for a specific country, significant refinement of intake estimates will be required based on known national food consumption data. To assist with this, all our model code is provided in the Appendix, which can be used by regulatory authorities to conduct risk assessments using local data.

4. Conclusions

A lognormal-operation-based regulatory modeling framework was developed to evaluate current pesticide MRLs in crops. Facilitated by the lognormal sum approximation and the lognormal product theorem, the proposed model can parametrically generate simulated exposure risks as a lognormal distribution. Under empirical conditions, the resulting SDIs are higher than existing conservative TMDIs, indicating that current theoretical MRLs may result in greater health risks than previously thought. Adopting the simple SDI distribution, our proposed model can also be adjusted using VFs to back-estimate pesticide residue levels and incorporates PFs for refining population-level aggregate pesticide exposure risk. As such, our modeling framework can be flexibly applied to a broad range of crops and scenarios. Building on this work, we hope that the proposed method can help optimize the MRL regulatory process.

Credit author contribution statement

Yuan Guo: Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. Zijian Li: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Resources, Project administration, Funding acquisition, Supervision, read and approved the final version of the article.

Fig. 6. Simulated daily intake (SDI, mg kg^{-1} d^{-1}) of chlorpyrifos and glyphosate based on the EU MRLs incorporating a point estimate and lognormal distribution of the processing factor (PF), plotted as a cumulative distribution function in comparison with the SDI without incorporating the PF.

Declaration of competing interest

The authors have declared that is no con...ict of interest in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.116832.

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