Residual dynamics and dietary exposure risk of dimethoate and its metabolite in greenhouse celery

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ABSTRACT

In recent years, residues of the insecticide dimethoate and its metabolites in fruits and vegetables, especially celery, have drawn attention to public health risks. We studied the residual dynamics and dietary risk of dimethoate and its metabolite omethoate in celery. We sprayed celery with 40% dimethoate EC at either a low concentration of 600 g a.i./ha or a high concentration of 900 g a.i./ha. Plants at the seedling, transplanting, or middle growth stages were sprayed once, and samples were collected 90 days after transplantation. Plants at the harvesting stage were sprayed 2 or 3 times. Samples were collected on days 3, 5, 7, 10, 14, and 21 after the last pesticide application. Finally, we extracted the dimethoate and omethoate compounds from the celery samples using acetonitrile and detected their concentrations using ultra-performance liquid chromatography-tandem mass spectrometry. We also conducted dietary risk assessments of dimethoate and omethoate in various populations and different foods in China. The results show that the metabolism made the omethoate present in the celery of dimethoate. Notably, the degradation dynamics of dimethoate and total residues in greenhouse celery followed the first-order kinetic equation. The half-lives of the compounds were 2.42 days and 2.92 days, respectively. The celery who received one application during the harvesting stage had a final residue of dimethoate after 14 days, which was lower than the maximum residue limit (MRL) 0.5 mg kg^{-1} for Chinese celery. And the final deposition of the metabolite omethoate after 28 days was less than the MRL 0.02 mg kg^{-1} for Chinese celery. Furthermore, after day 21, the RQs of dimethoate in celery was less than one, so the level of chronic risk was acceptable. Only children aged 2-7 years had an HQ of dimethoate over 1 (an unacceptable level of acute risk), while the critical dietary risks to other populations were within acceptable levels. We recommend that any dimethoate applications to celery in greenhouses should happen before the celery reaches the harvesting stage, with a safety interval of 28 days.

Keywords Celery, Dimethoate, Omethoate, Pesticide residues, Dietary risk assessment

INTRODUCTION

Celery is a good source of vitamin C, folic acid, carotene, phenols, and flavonoids (*Liang et al., 2018*) – which are known to lower blood pressure (*Madhavi et al., 2013*) and have anti-inflammatory and antioxidant effects in humans and other mammals (*Kooti et al., 2017*; *Powanda et al., 2011*). China ranks first in the world for celery

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production with a planting area of around 550000 ha (*Gao et al., 2014*; *Madhavi et al., 2013*). Pesticides are commonly used in celery production to increase crop yield and quality by preventing and reducing the damage caused by diseases and insect pests. However, the application of pesticides has potential risks to the environment and human health, so risk assessments of pesticide residues have received increasing attention (*Dai et al., 2019*; *Dominiak 2019*; *Kranawetvogl et al.*, 2018; Rezaei & Mahdi, 2018).

Omethoate is a highly toxic pesticide with strong contact and penetration effects (*Eddleston et al.*, *2016*; *Zhang et al.*, *2017*), and it has been banned from use on vegetables in China. However, recent investigations found that the detection rate and over standard rate of this pesticide residues are relatively high in celery (*Liu*, *2017*; *Sun et al.*, *2014*; *Yaojun et al.*, *2016*). The investigation concluded that the primary cause of this problem might be that celery sprayed with dimethoate produce omethoate as a metabolite. Dimethoate, a broad-spectrum systemic insecticide, and acaricide are widely used to control insect pests in vegetables, fruits, tea trees, wheat, and rice (*Zheng & Sun*, *2014*).

Omethoate is a metabolite of dimethoate. Its toxicity is much higher. In China, the safety interval after the dimethoate application is 14 days. Notably, previous research showed that, for the residue of omethoate to be below the maximum residue limit (MRL), the safety interval for celery sprayed with dimethoate should be 21 d (*Guo et al.*, *2017*). Nevertheless, with the improvement of peoples' standard of living, the demand for fresh vegetables in winter increases, resulting in the expansion of the celery planting area in northern greenhouses and greater use of dimethoate. Besides, whether the current safety interval for dimethoate application ensures the residue of its metabolite omethoate below the MRL is not clear. Therefore, it is vital to monitor dimethoate and omethoate residues in greenhouses to assess human health risks (EFSA, *2016*; *Van et al.*, *2016*; *Zhu et al.*, *2015*).

Although efforts have been put into studying the dynamics of dimethoate in celery (*Chen et al.*, *2018*; *Lu et al.*, *2017*; *Yuan et al.*, *2014*), there are few reports on the degradation dynamics of omethoate residues. Here, we investigated the dissipation dynamics and residues of dimethoate and omethoate in greenhouse celery. Based on the experimental data, we conducted dietary risk assessments for different populations in China, and the safe application of dimethoate in celery was explored.

MATERIALS AND METHODS

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Test materials

Celery was used as the test crop. The field test was carried out in the vegetable production base in Liaozhong district of Shenyang City. There were no extreme weather events during the pesticide applications, such as heavy rain and hail, and the climatic conditions were normal. The test pesticide was 40% Dimethoate EC. The maximum recommended dose is 600 g a.i./ha in China, Hebei Zhongtian Bangzheng Biologic Science Co., Ltd., Before application, the formulation of dimethoate was analyzed. The content of dimethoate met the requirements, and no omethoate was detected in it.

Instruments

Waters UPLC TQ Ultra Performance Liquid Chromatography-Tandem Mass Spectrometer, Waters, USA; Zhongjia HC 3514 High-Speed Centrifuge, Anhui USTC Zonkia Scientific Instrument Co., Ltd.; Ding Haoyuan RS-1 Vortex Mixer, Beijing Ding-Hao Yuan Technology Co., Ltd.; Pine-tree ultra-pure water machine, Beijing Xiangshunyuan Technology Co., Ltd.; JACTO HD400 Backpack Sprayer, JACTO Agricultural Machinery Co., Ltd.; 0.22 µm needle filter, 50 mL polypropylene plastic centrifuge tube, Xinkang Medical Equipment Co., Ltd.

Reagents

Methanol, acetonitrile (chromatographically pure), Merck. Wondapak QuEchERS extraction and separation kit, Shimadzu Kojima (Shanghai) Trading Co., Ltd. Dimethoate and omethoate were purchased from the Environmental Quality Supervision and Testing Center of the Ministry of Agriculture (Tianjin).

Standard solutions

Standard stock solutions (100 mg L^{-1}) of dimethoate and omethoate was diluted with acetonitrile to make the working standard solution comprised (0.005, 0.01, 0.02, 0.05, 0.1, 0.2 and 0.5 mg L^{-1}) . Additionally, celery samples cultivated in control plots were used as blanks. The stock solution was diluted with the clean control extract to generate the matrix standard solution (0.005, 0.01, 0.02, 0.05, 0.1, 0.2 and 0.5 mg L^{-1}). Standard solutions were stored in the dark at -20°C. Blanks with a dimethoate and omethoate solution at three concentration levels (0.01, 0.1, and 1 mg kg^{-1}) were employed for the recovery assay. The analytical method's performance parameters were determined in addition to recovery rates, such as linear ranges, LOQ, and LOD.

Field test design

According to Guideline's requirements on pesticide residues trials (NY/T 788-2004,

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2004), the test plot was designed with a plot area of 30 m^2, a buffer zone of 2 m, and three repeat plots, which were randomly arranged. A control area of 30 m^2 without pesticide application was also set up to collect control samples.

Dissipation dynamics: Dimethoate sprayed at 900 g a.i./ha (1.5 times the maximum recommended dose) using a knapsack sprayer on the surface of celery at the moderate growth stage, and the experiment was repeated on three plots. Samples were collected at two h, 1 d, 3 d, 5 d, 7 d, 10 d, 14 d, 21 d, 28 d, and 42 d after pesticide application.

Final residual dynamics: The pesticide application dose was 600 g a.i./ha (the maximum recommended dose) and 900 g a.i./ha (1.5 times the maximum recommended dose), respectively. Dimethoate sprayed once using a knapsack sprayer on the soil at the seedling stage, and ripe celery samples were collected at 145 days after the pesticide application. Dimethoate sprayed once using a knapsack sprayer on the surface of celery at the transplanting stage, and ripe celery samples were collected at 90 days after the pesticide application. Dimethoate sprayed once using a knapsack sprayer on the celery surface at the middle growth stage, and samples of ripe celery were collected at 45 days after the pesticide application. Besides, dimethoate sprayed using a knapsack sprayer on the surface of celery 2 and 3 times during the harvesting stage with intervals of 7 d between applications, and the experiment was repeated on three plots. Samples were collected at 3 d, 5 d, 7 d, 10 d, 14 d, and 21 d after the last pesticide application.

The seedling stage is the day of sowing, the transplanting stage is 55 days after sowing, while the middle growth stage is 45 days after transplantation. Finally, ripe celery was collected 90 days after transplantation. The harvesting stage is 62-97 days after transplantation. Samples were collected at 3 d, 5 d, 7 d, 10 d, 14 d, and 21 d after the last pesticide application. The growing stage, day of the pesticide application, and sampling are shown in Figure 1.

Sampling: 2 kg of standard, damage-free celery samples of 2 centimeters above the ground were randomly collected from 5-12 points in each plot each time. No samples were collected within 0.5 m of the edge of the field. The samples were placed in polyethylene bags and transported to the laboratory for the next study stage. Samples were homogenized using a blender (Foer Group, Hong Kong Special Administrative Region, China) and stored in a refrigerator at -18°C until use.

Sample analysis

Extraction: Firstly, 10.0 g of the sample to be tested was weighed and placed in a 50

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mL centrifuge tube. Secondly, 20.0 mL acetonitrile was added into the centrifuge tube and homogenized for 2 min. The QuEChERS extraction separation bag was added with vigorously shaking for 2 min and centrifuged at 10,000 r/min for 5 min. Lastly, the solution supernatant was filtered with 0.22 μm filter membrane, and the filtrate was ready to be tested.

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Detection

Chromatographic conditions: Acquity UPLC HSS T3 column (100 mm × 2.1 mm, 1.8 μm), column temperature 25 °C, injection volume 5 μL, flow rate 0.38 mL min^{-1}, mobile phase A is water, and B is methanol. Gradient elution conditions: 0 - 0.25 min, 90% - 5% A; 0.25 - 5.00 min, 5% - 90% A. Mass spectrometry conditions: electron spray ion source positive ion mode (ESI +), ion source temperature 500 °C, capillary voltage 1.0 kV, nebulizing gas flow rate 900 L h^{-1}, taper hole anti blow air flow rate 50 L h^{-1}, and the scanning method was the multiple reaction monitoring (MRM) mode. The other MS/MS parameters were separately optimized for each target compound and are listed in Table 1.

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Dissipation dynamics

The first-order kinetic equation was used to express the dissolution dynamics of dimethoate and omethoate in celery over time.

$$c_t = c_0 e^{-kt} \qquad (1)$$

$$t_{1/2} = \frac{Ln2}{k} \qquad (2)$$

Where t is time (day), c_t is the concentration (mg kg^{-1}) at time t (days), c_0 is the initial concentration (mg kg^{-1}), k is the degradation rate constant (day^{-1}), and $t_{1/2}$ is the half-life (d).

Final residue

The toxicological endpoints of dimethoate and its metabolite are the same, so the sum of residues of dimethoate and omethoate should be considered together for both acute and chronic dietary intake. Omethoate is more toxic than dimethoate, and the relative toxicity of omethoate compared to dimethoate following chronic and acute were found to be about ~3:1 and ~6:1, respectively (None, 2009).

Sum of dimethoate and 6*omethoate, expressed as dimethoate (for acute risk assessment);

Sum of dimethoate and 3*omethoate, expressed as dimethoate (for chronic risk assessment).

The risk of acute dietary exposure consists of a WHO template for evaluating acute exposure (IESTI). In contrast, the risk of chronic dietary exposure uses a WHO template to evaluate chronic exposure (IEDI). (http://www.who.int/foodsafety/areas_work/chemical-risks/gems-food/en/).

The following formula (*Geng et al.*, *2018*) was used to calculate the risk of chronic dietary exposure of dimethoate and omethoate.

$$NEDI = F \times STMR / bw \qquad (3)$$

$$RQ = NEDI / ADI \qquad (4)$$

Where $NEDI$ is the country's estimated daily intake (mg kg^{-1} bw day^{-1}), $STMR$ is the median residue of the standard test (mg kg^{-1}), F is the average food consumption (kg d^{-1}), bw is the body weight (kg), and ADI is the acceptable daily intake (mg kg^{-1} bw day^{-1}). RQ Is chronic risk assessment, $RQ>1$ indicates that the chronic dietary intake risk is unacceptable; $RQ<1$ suggests that the chronic nutritional intake risk is acceptable, and the smaller, the smaller the risk.

The following formula was used to calculate the risk of acute dietary exposure of dimethoate (the single weight of unprocessed food was over 25 g, and the edible portion's available weight was over or equal to the consumption of most individuals) (Geng et al., 2018).

$$IESTI = LP \times HR \times v / bw \qquad (5)$$

$$HQ = IESTI / ARfD \qquad (6)$$

Where $IESTI$ is the estimated short-term intake(mg kg^{-1} bw day^{-1}), LP is the average food consumption(kg d^{-1}), HR is the highest residue obtained in the test (mg kg^{-1}), v is the variability factor and was assigned a value of 3 according to JMPR (*Gao et al.*, *2007*), bw is the body weight (kg), and $ARfD$ is the acute reference dose mg (mg kg^{-1} bw day^{-1}). HQ is acute risk assessment， when $HQ<1$, which means that the risk of acute dietary intake is acceptable. $HQ>1$, it means that there is an unacceptable acute risk.

RESULTS

Method validation

The limits of detection (LODs) and the limits of quantification (LOQs) for dimethoate and omethoate were considered to be the concentrations produced at a signal-to-noise (S/N) ratio of 3 and 10, respectively. The LODs for the two target chemicals were 0.003

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mg kg^{-1}, and the LOQs were 0.01 mg kg^{-1}. Good linear calibration curves were obtained over the concentration range of 0.005 - 0.5 mg L^{-1} for dimethoate and omethoate and the correlation coefficient r was higher than 0.99 (Table 2). The sample concentrations outside the linear range are diluted to the appropriate analytical concentration. The matrix effect (ME) was calculated:

$$ME\ (\%) = (\text{slope ratio} - 1) \times 100\% \quad (7)$$

$$slope_{ratio} = slope_{matrix} / slope_{solvent} \quad (8)$$

where slope matrix and slope solvent are the calibration curve slopes of the celery and acetonitrile standard, respectively. The matrix effects (MEs) were -4% (Table 2), which caused the signal's suppression. Thus, matrix-matched calibration solutions were used to compensate for errors associated with matrix-induced calibration.

The accuracy was evaluated by determining the recovery assay at three levels in celery. No dimethoate and omethoate were detected in the blanks. The mean recoveries were 83.4%-92.9% and 80.4%-94.6% for dimethoate and omethoate, with RSD in the range of 3.7%-4.5% and 4.0%-7.3%, respectively (Table 3). This evidence demonstrates that the method of analysis is accurate and precise.

Dimethoate dissipation dynamics in celery

The results of dimethoate detection are given as average values of three repeat plots. As shown in Figure 2 (when the safety interval was over 28 d, the concentration of dimethoate was lower than the LOQ.), the degradation of dimethoate met the first-order kinetic equation, $Ct = 4.0499\ e^{-0.286t}$, and the correlation coefficient R^2 was 0.9943. The half-life was 2.42 d, it indicates dimethoate is an easily degradable pesticide. Ten days later, the dissipation rate reached 94.6%, and the residual concentration of dimethoate decreased below 0.5 mg kg^{-1} (the MRL of dimethoate on celery is 0.5 mg kg^{-1}), which is lower than the MRL. Furthermore, the dissipation rate reached 99% after 16.1 d.

Omethoate dissipation dynamics in celery

The results of omethoate detection are given as average values of three repeat plots. The dissipation data fitting is shown in Figure 3 (when the safety interval was over 42 d, the concentration of omethoate was lower than the LOQ.). Before application, the formulation of dimethoate had been analyzed, and no omethoate was detected in it. But omethoate was detected in the celery. After the application of dimethoate, the concentration of omethoate increased to 0.19 mg kg^{-1} on day three, and gradually decreased after 3 days. This indicated that the high levels of omethoate present in the celery were made by dimethoate metabolism. After day 28, the omethoate concentration

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was below 0.02 mg kg^{-1}, which is lower than the allowable MRL of omethoate in celery. These findings demonstrate that a 10 d safety interval is sufficient to ensure the dimethoate concentration in celery declines to safe levels but is not enough for the omethoate concentration to reach safe levels. Based on the MRL (0.02 mg kg^{-1}) of omethoate in Chinese celery, we recommend a safety interval of 28 d after dimethoate application.

As shown in Figure 4, the dissipation behavior of total residues of dimethoate and its metabolite omethoate conformed to the first-order kinetic equation, $C_t = 3.7599e^{-0.237t}$, the correlation coefficient r^2 was 0.9814. The half-life was 2.92 d, which is 20.1% longer than that of parent compound dimethoate. This indicated that as a metabolite of dimethoate, omethoate should be taken into account in risk assessment.

Final residues following pesticide treatments in seedling, transplanting, and middle growth stage

The final residues of dimethoate and its metabolite omethoate after application during the seedling stage, transplanting stage, and middle stage of the celery growth are shown in Table 4. The data show that both residues of dimethoate and omethoate in celery were lower than the LOQ and the MRLs (the MRL of dimethoate is 0.5 mg kg^{-1} and the MRL of omethoate is 0.02 mg kg^{-1}).

Final residues following pesticide treatments in the harvesting stage

Samples were collected at 3 d, 5 d, 7 d, 10 d, 14 d, and 21 d after the last pesticide application. The final residues of dimethoate and omethoate are shown in Table 5–6. The data show that, when two different dosages of dimethoate were sprayed 2 or 3 times, the residue of dimethoate in celery was lower than the allowable MRL of 0.5 mg kg^{-1} at 10 d. However, omethoate concentration was still higher than the allowable MRL of 0.02 mg kg^{-1} at 21 d. Additionally, celery sprayed three times with the same dimethoate concentration had higher residues of dimethoate and omethoate than celery that was only sprayed twice, showing a cumulative effect of repeated pesticide application. However, because we did not collect a sample of celery 28 d after the final pesticide application, we were unable to determine whether the concentration of omethoate had declined to a level below the MRL by this stage.

Chronic dietary risk assessment

Although we recommend the safety interval (based on the MRL of omethoate in Chinese celery, we recommend a safety interval of 28 d after dimethoate application). The dietary intake risk had not been calculated at different times. Based on our test

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As shown in Figure 3, the degradation of omethoate conformed to the first-order kinetic equation, $Ct = 0.1623e^{-0.084t}$, the correlation coefficient r was 0.971, and the half-life was 8.25 d. It is worthy of note that after the application of dimethoate, the concentration of Omethoate then gradually increase as the dimethoate degrades and gradually decrease after 3 days. It is a complex time-conc, the degradation of omethoate from the third day more conformed to the first-order kinetic equation. Moreover, after 28 d, the concentration of omethoate was below 0.02 mg kg^{-1} and the dissipation rate reached 93%, which is lower than the allowable MRL of omethoate in celery. Furthermore, after 54.7 d, the dissipation rate reached 99%. These findings demonstrate that a 10 d safety interval is sufficient to ensure the dimethoate concentration in celery declines to safe levels but is not sufficient for the omethoate concentration to reach safe levels. Based on the MRL (0.02 mg kg^{-1}) of omethoate in Chinese celery, we recommend a safety interval of 28 d after dimethoate application

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data, the standard median residue test (STMR) of the total of dimethoate and omethoate in celery is shown in Table 7. The allowable daily intake (ADI) of dimethoate is 0.002 mg kg^{-1} bw (*GB 2763-2016, 2016*). The daily consumption of vegetables is known based on the Chinese dietary structure (*Wu et al., 2018; Liu et al., 2018*). The daily intake of celery was lower than the total vegetable intake. Suppose the daily total vegetable intake replaces the celery intake. In that case, the calculated dietary risk of the total residual of dimethoate and omethoate is acceptable in vegetables. The dietary risk of the total residual of dimethoate and omethoate in celery is acceptable.

The risk quotient (RQ) was calculated according to the chronic dietary risk formula 3 and 4. The results show (Table 7) that on day 10, the RQs of dimethoate were more than one and therefore, the risks were unacceptable. Day 14, some RQs of dimethoate were more than 1 (2-12 years and 51-65 years/female), and the chances were considered to be unacceptable. After day 21, the RQs of dimethoate in celery were less than one, so the level of chronic risk was acceptable.

Acute dietary risk assessment

The acute reference dosages (ARfD) of dimethoate is 0.01 mg kg^{-1} bw (*Geng et al.*, *2018; Utture et al.*, *2012*). Based on the dietary structures of different populations in China (*Wu et al.*, *2018*), the HQ was calculated according to the acute dietary risk assessment formula 5 and 6 to judge the level of critical dietary risk (Table 8). The results show that on the 10th day, the HQ range of dimethoate was 2.42-4.15. On day 14, the content of the HQ of dimethoate was 1.22-2.09. On day 21, the HQ range of dimethoate was 0.67-1.14. Day 10 and 14, the HQs of dimethoate were more than one, and the acute risks were unacceptable. On day 21, only children aged 2-7 years had an HQ of dimethoate over 1 (an intolerable level of risk), while the acute dietary threats to other populations were within acceptable levels. As a precaution, we recommend that diets for children aged 2-7 avoid large amounts of single types of food in the short term to reduce acute dietary risk.

DISCUSSION

This study found that the dissipation of dimethoate and total residues in greenhouse celery conforms to the first-order kinetic equation, with R^2 equal to 0.9943 and 0.9814, respectively, and half-lives of 2.42 d and 2.92 d, respectively.

Previous studies found that the half-lives of dimethoate in the open field are 2.5 d (*Guo et al.*, *2017*), indicating that the residual periods of dimethoate were no significant difference in the greenhouse area. According to reports, the half-life of

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Deleted: and omethoate in greenhouse-grown crops may be longer and require longer safety intervals dimethoate in mango is 2 d (*Bhattacherjee et al.*, *2016*), and the half-life in cucumber is 5.2 d (*Geng et al.*, *2018*), which indicates that the dissipation of dimethoate is related to the matrix it is applied to. The half-life of dimethoate in celery grown in Guizhou is 5.4 d, and the half-life of celery in Anhui is 3.5 d (*Chen et al.*, *2018*). Nevertheless, 7 d after application, the dissipation rate of dimethoate is faster in Liaoning (85%) than in Guizhou (75%) and Anhui (70.27%), indicating that the half-life of dimethoate is also related to region and climate.

As shown in the final residue results, spraying dimethoate's safety risks during the seedling, transplanting, and moderate growth stages are within acceptable limits. Specifically, 14 d after the last application during the harvesting stage, the residue of dimethoate dropped below its MRL. Still, the residue of the dimethoate metabolite omethoate remained far higher than its MRL. Hence, dimethoate application's safety interval should be at least 28 d, which is similar to the respective safety intervals of 27 d for cucumber (*Geng et al.*, *2018*), and 30 d for pomegranate (*Utture et al.*, *2012*).

As shown by the results of the dietary risk assessments, after day 21, the RQs of dimethoate in celery were less than one and so the level of chronic risk was acceptable. Only children aged 2-7 years had an HQ of dimethoate over 1 (an unacceptable level of acute risk), while the critical dietary risks to other populations were within acceptable levels. Furthermore, from a toxicology perspective, the celery would be safe to eat at this safety interval even if the residual concentration of omethoate in celery was higher than the corresponding MRL. Poland and France have made similar assessments of exposure risks to dimethoate and omethoate in other foods (*Nougadère et al.*, *2014*; *Paweł et al.*, *2015*).

CONCLUSION

This study shows that the application of dimethoate to greenhouse-grown celery results in omethoate residues that exceed acceptable levels after the current standard safety interval. Any applications of dimethoate to celery in greenhouses will occur with a 28-day safety interval that ensures adequate of residue omethoate. As a precaution, it is recommended that diets for children 2-7 years of age avoid large amounts of single types of food to reduce their dietary risk. Notably, this result provides data to support risk assessments of dimethoate and omethoate in celery and other foods. Although the standard residue test in this study was conducted in the Liaoning district, it references other regions in northern China. More importantly, the multi-year residual data in many places may be combined to make these assessments more accurate.

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