



Original Research Article

Pesticides, metals, and polycyclic aromatic hydrocarbons in date fruits: A probabilistic assessment of risk to health of Iranian consumers



Seyedeh Faezeh Taghizadeh^{a,b,1}, Ramin Rezaee^{c,d,1}, Majid Azizi^a, A. Wallace Hayes^{e,f}, John P. Giesy^{g,h,i}, Gholamreza Karimi^{b,j,*}

^a Department of Horticultural Science, Ferdowsi University of Mashhad, Mashhad, Iran

^b Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

^c Clinical Research Unit, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

^d Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

^e University of South Florida College of Public Health, Tampa, FL, USA

^f Michigan State University, East Lansing, MI, USA

^g Department of Veterinary Biomedical Sciences and Toxicology Centre, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

^h Department of Environmental Sciences, Baylor University, Waco, TX, USA

ⁱ Department of Zoology and Center for Integrative Toxicology, Michigan State University, East Lansing, MI, USA

^j Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

The present study assessed the risk posed by simultaneous oral exposure to a mixture of 22 pesticides, 6 metals, and 16 Polycyclic Aromatic Hydrocarbons (PAHs) in fruits of date palms, to Iranian consumers. Various cultivars of dates were collected from six regions in Iran. Concentrations of organic compounds and metals in 900 samples of date fruits were quantified by chromatography-mass spectrometry (GC-MS) and inductively coupled plasma-optical emission spectrometry (ICP-OES), respectively. No significant associations between any of the contaminants and cultivation zones were observed. Calculated Hazard Quotients (HQ) was <1.0 for all pesticides and calculated total Hazard Index (HI) values indicated no major risk. For the carcinogenic metals, estimated Incremental Life Time Cancer Risk (ILCRs) at the 50th and 95th percentiles were respectively 2.25×10^{-7} and 7.10×10^{-7} for As, and respectively 1.24×10^{-9} and 5.38×10^{-9} for Pb which indicated no risk. Notably, non-carcinogenic metals did not exhibit a significant risk (HI values <1.0 for both cases). In addition, at the 50th and 95th percentiles, ILCR and Margins of Exposure (MoE) for PAHs indicated no risk. Based on sensitivity analysis, concentrations of analytes had the greatest effects on risk with regard to carcinogenic and non-carcinogenic assessment endpoints. However, consumers are aware of the composition of the fruits they eat, because harmful substances in fruits normally cannot be perceived by tasting or smelling. It can also be noted that general awareness of Iranian farmers need to be upgraded for a more cautious utilization of pesticides and fertilizers in agricultural practices. Moreover, our results about the PAHs indicated that the consumption of dates grown near the industrial sites is risky and should be completely avoided.

1. Introduction

Assessment of risk posed to humans health via exposure to mixtures of chemicals is challenging (Amini et al., 2014; Béchaux et al., 2013). In daily life, humans and animals are exposed to mixtures of chemicals with different modes of action. Methods of traditional health risks

assessments (HRA) were developed for a single chemical and one route of exposure, ignoring potential interactions -that may alter toxic potencies- between chemicals (Heys et al., 2016). Increasing awareness about synergistic or antagonistic effects of components, has forced risk assessors and several international regulatory authorities to consider different scenarios and develop new methodologies. For instance, the

* Corresponding author at: Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, P. O. Box, 1365-91775, Iran.

E-mail address: Karimig@mums.ac.ir (G. Karimi).

¹ These authors contributed equally to this work.

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European Food Safety Authority (EFSA) adopted a flexible overarching framework to harmonize methodologies for HRA of combined exposure. Assessing risks of combined exposure to multiple chemicals are conducted using both deterministic and probabilistic approaches (Rotter et al., 2018). Nevertheless, application of deterministic HRA tends to underestimate risks and provides a single-point estimate of individual risks and compared to probabilistic methods, it predicts lesser harm (Koupaie and Eskicioglu, 2015). Among all available techniques, Monte Carlo Simulation (MCS) is used as a mathematical model to estimate distribution of risk cross the population. Hence, probabilistic methods can potentially provide more useful estimates of risk (Richardson, 1996). HRA of chemicals requires a proper framework that takes different aspects including various sources of contaminants and potential interactions between the mixture components (e.g. synergistic, antagonistic, additive, potentiating, and inhibiting), into consideration. Probabilistic approaches significantly improve hazard assessment of complex mixtures (Hayes et al., 2019). Fruits and vegetables such as table olive, date, fig, kumquat, karambolas, kaki, and jambuls are classified as edible peel fruits (http://www.fao.org/infoods/tagnames_en.stm). Besides, the EFSA suggested a similar categorization when assessing risks posed by exposure to contaminants in such fruits and vegetables (EC, 2020).

Crops can absorb different contaminants from polluted soils, waters, and air. In fact, though very low concentrations of pesticides are being applied for pest removal, marked concentrations might accumulate in the crops and find their way to the environment and food chain. This is more common in case of edible peel fruits or crops that are close to table. Procedures including peeling, blanching, and cooking can reduce or remove residues (Liu et al., 2013; Sapbamrer and Hongsibsong, 2019).

Date palm (*Phoenix dactylifera* L.) cultivated in dry and semi-arid regions, is an important member of the family Palmaceae. Dates are rich in certain nutrients and provide a good source of rapid energy due to their high carbohydrate content (70–80 %). Most of the carbohydrates in dates are in the form of fructose and glucose which are easily absorbed by the human body. Also, the fruit is a good source of fiber, carbohydrates, minerals and vitamins, and has anti-mutagenic and anti-carcinogenic properties (Abu-Shama et al., 2020).

Exposure to pesticides can cause various toxic effects, including hepatotoxicity, nephrotoxicity, reproductive and developmental toxicity, cancers, behavioural changes, and Alzheimer's and Parkinson's disease as well as immunological, cardiovascular and respiratory conditions, in humans (Georgiadis et al., 2018; Hernández et al., 2013; Taghizadeh et al., 2019b).

In recent years, researchers have developed rapid multi-residue analysis methods. These techniques quickly analyze many compounds thus more food samples can be examined for a larger number of pesticides. The multi-residue methods overcome challenges of screening a very large number of samples for a variety of chemical compounds; so, these types of techniques have been implemented into regular testing programs in recent years. To improve the efficiency of traditional methods, a new sample preparation approach called QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe), was introduced (Anastassiades et al., 2003; Qin et al., 2016b). This method was initially developed for fruits and vegetables which contain plenty of water. Originally, QuEChERS was a particular "method" for pesticide residue analysis, but it is very flexible and has evolved into an "approach," which has been used in many methods, and not just for pesticide residues. The main aspects of the QuEChERS approach consists of extraction of a well-homogenized sample by shaking with solvent (typically acetonitrile) in a centrifuge tube, salt-out partitioning of water with salts including magnesium sulfate (MgSO₄), and cleanup using "dispersive solid-phase extraction" (dSPE), in which common matrix components are retained by sorbent(s) and the analytes remain in the extract. QuEChERS extract was found to be enough to remove phenolic components from the tested fruits and vegetables (Lehotay, 2011; Qin et al., 2016a).

In co-exposure to multiple metals, their interactions not only affect the way they are absorbed or metabolized but also influence their distribution, and excretion (Bárány et al., 2002). Importantly, entrance of metals into the soil from various sources like contaminated irrigation water, use of metal-based pesticides and fertilizers, and harvesting and post-harvesting procedures can potentially introduce them into the food chain causing major health concern (Aminifard et al., 2012; Wang et al., 2015). Arsenic (As) is classified as a human carcinogen (Group 1) while lead (Pb) is classified as a probable human carcinogen (Group 2A) by the International Agency for Research on Cancer (IARC) (IARC, 2017). Mercury (Hg), especially methyl mercury (MeHg), is recognized as a neurotoxicant and a bio-accumulating metal. Cadmium (Cd) is characterized as a Group 1 human carcinogen by IARC (Azizi and Omidbaigi, 2001; Fakhri et al., 2018; Renieri et al., 2019). Cadmium (Cd) contamination occurs mainly due to extensive use of phosphate fertilizers and because of its relative mobility, high solubility in water, and extended half-life (> 20 years) (Heidari et al., 2014; Ji et al., 2017; Wang et al., 2020). IARC has categorized metallic chromium (Cr) and Cr (III) as Group 3 carcinogens with Cr (IV) being classified as a Group 1 human carcinogen (IARC, 2017; Ni et al., 2020; Zong et al., 2020). Cr is poorly biodegraded and it readily accumulates in plants, most commonly as Cr (III) and Cr (IV). The latter is highly soluble in water and can be transferred along the food chain. Phosphate fertilizers and pesticides significantly increase nickel (Ni) concentration in the soil. Ni toxicity induces oxidative stress and DNA damage and can cause respiratory allergies and cancers. IARC classifies Ni as a Group 2 B carcinogen (IARC, 2017; Rehman et al., 2018).

PAHs including nitro-PAHs, and oxy-PAHs are known as carcinogenic and/or mutagenic chemicals (Santos et al., 2017; Srivastava et al., 2018). They induce reactive oxygen species (ROS) overproduction and cause oxidative stress. Compared to heavy PAHs, it is easier for PAHs of lower molecular mass to enter an aquatic matrix (Nascimento et al., 2019). The United States Environmental Protection Agency (USEPA) considers the following 16 PAHs as the major contaminants in foods: Naphthalene (Nap), Fluorene (Fl), Acenaphthylene (Acy), Phenanthrene (Phe), Acenaphthene (Ace), Anthracene (Ant), Fluoranthene (Flu), Benzo[a]Anthracene (BaA), Pyrene (Pyr), Chrysene (Chr), Benzo[b]Fluoranthene (BbF), Benzo[g,h,i]Perylene (BghiP), Benzo[k]Fluoranthene (BkF), Benzo(a)Pyrene (BaP), Indeno[1,2,3-cd]pyrene (IcdP), and Dibenzo[a,h]anthracene (DahA). Among these PAHs, BaP and DahA were classified as established carcinogen (Group 1) and probable carcinogen (Group 2A), respectively (Kermani et al., 2019; Yousefi et al., 2018). As recommended by the Food and Agriculture Organization of the United Nations (FAO) and the Scientific Committee on Food (SCF), monitoring PAHs in food is necessary to guarantee human health (Pisinnatti et al., 2015).

Most of the date orchards in Iran are located in industrialized areas, even near oil refineries such as Abadan refinery or near road ways. Moreover, several orchards are irrigated with wastewater. Based on previous reports, PAHs showed higher levels in infected zones compared to the rural areas (Paris et al., 2018).

The current study presents: (i) concentrations of 22 pesticides, 8 metals, and 16 PAHs in various cultivars of dates collected from six cultivation zones of Iran and (ii) results of carcinogenic and non-carcinogenic HRA, based on IARC classifications, and (iii) input parameters that had the greatest impact (based on sensitivity analysis) on the HRA. To the best of our knowledge, this is the first HRA of oral exposure to chemical mixtures comprised of pesticides, metals and PAHs, through consumption of dates.

2. Material and methods

2.1. Chemicals

All standards (of 99 % purity) were purchased from Sigma-Aldrich (Steinheim, Germany). Solvents (HPLC grade) including ethyl acetate

(EtOAc), acetonitrile (MeCN), nitric acid (HNO₃), dichloromethane, tetrahydrofuran and n-hexane were purchased from Merck (Darmstadt, Germany) and Sigma-Aldrich (Steinheim, Germany). Anhydrous sodium sulfate (99 % purity; BDH, Poole, UK) and Sep-Pak silica plus long cartridges (690 mg sorbent per cartridge; 55–105 µm particle size; Waters, Wexford, Ireland) were also used.

2.2. Sample collection

A total of 900 samples of the major date fruit cultivars consumed in Iran, were collected from 6 main important cultivation zones ((Abadan (Khuzestan province), Bam (Kerman province), Dashtestan (Bushehr province), Jahrom (Fars province), Minab (Hormozgan province), and Saravan (Sistan va Baluchestan province)). Ten most common and popular cultivars (including Barhi, Deri, Estamaram, Kabkab, Mazafati, Medjool, Piarom, Rabbi, Shahani, and Zahedi) were harvested seasonally (during the fruiting season) in 2018 and 2019. Three samples of each of the 10 cultivars, were randomly collected from 5 different orchards of each of the 6 cultivation zones [(10 cultivars) × (6 zones) × (5 orchards in each zone) × (3 replicates) = 900 samples] (Fig. 1).

2.3. Samples preparation

To avoid any cross-contamination, collected samples were kept in polyethylene bags, and immediately transferred to the laboratory within 12 h and were stored at −20 °C until analysis. The samples were rinsed with deionized water and oven-dried at 45 °C. Then, fresh and dry mass was measured before and after drying, respectively. The samples were grounded, passed through 2-mm mesh size sieves, packed in polyethylene covers, and stored at −20 °C until analysis (Ghasemidehkordi et al., 2018; Medina et al., 2020; Wang et al., 2012; Xu et al., 2020; Yang et al., 2020).

For in-lab contamination reduction, bench was pre-cleaned with oxygen peroxide (30 %) and all material used (beaker, crucibles, tips, tubes, etc.) were pre-rinsed with nitric acid (20 %).

2.4. Instrumentation

2.4.1. Gas chromatography-mass spectrometry (GC-MS) for pesticides analysis

An Agilent 7890A Turbo MSD 5975C (Agilent, Santa Clara, USA) was used; The GC-MS system was equipped with a programmable temperature vaporizer (PTV) inlet and 7683B auto injector. The carrier gas was helium (at a flow rate of 1.0 mL/min). The system was equipped with an HP-5 MS (30 m × 0.25 mm × 0.25 µm) column (Agilent, Santa Clara, USA.). The temperature program was the following: initial temperature 70 °C held for 1 min, 10 °C/min ramp to 130 °C, then 6 °C/min to 230 °C, finally by 8 °C/min to 250 °C held for 13 min. The temperature

of the injection port was 250 °C and a 1 µL volume was injected. Electron ionization (70 eV) with selected ion monitoring mode was used, and the most abundant ion from the molecular ion cluster was measured for each analyzed compound. The quadrupole analyzer measured the abundance of ions of *m/z* from 50 to 490 (detector voltage 1294 V). Pesticides were identified based on comparisons of observed GC retention time with those of standard solutions of pesticides and use of characteristic ions (Chizzola et al., 2014; Shakeri et al., 2019; Taghizadeh et al., 2019a).

2.4.2. Gas chromatography-mass spectrometry (GC-MS) for PAHs analysis

Identification and quantification were accomplished by use of Agilent 6890 N (Agilent, Waldbronn, Germany) gas chromatography (GC) coupled with an Agilent 5975 quadrupole mass selective spectrometer equipped with an inert ion source and a split-splitless injection port. A DB-5MS (Agilent) capillary column (5 % diphenyl- 95 % dimethyl polysiloxane of 30 m × 0.25 mm i.d., with 0.25 µm film thickness) was used. Operating conditions were as follows: helium was the carrier gas (1.5 mL/min constant flow); injector temperature was 300 °C, pulsed splitless, injection volume was 1 µL; the ion source, transfer line, and quadrupole temperatures were 300, 280, and 180 °C, respectively; and GC oven temperature program was 55 °C (1 min), and 55–290 °C (25 °C/min for 3 min). The quadrupole analyzer measured the abundance of ions of *m/z* from 45 to 450 (detector voltage 1294 V). Electron ionization (70 eV) with selected ion monitoring mode was used, and the most abundant ion from the molecular ion cluster was measured for each analyzed compound (Szelewski, 2005). PAHs were identified based on comparisons of observed GC retention time with those of standard solutions of PAHs and use of characteristic ions (Badibostan et al., 2019).

2.4.3. Microwave digestion and inductively coupled plasma-optical emission spectrometry (ICP-OES)

For quantification of metals, microwave digestion system (Milestone Ethos Microsynth Oven, Germany) was used for homogenized samples with 10 W intervals and 1000 W maximum power. Digestion conditions are reported in Table 1 (Akbari et al., 2012). Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) (SPECTRO ARCOS, Germany) was used for simultaneous multi-element detection with Torch type of Flared end EOP Torch 2.5 mm. The plasma power was 1.2 kW, the argon flow rate was 15.0 L/min with an auxiliary flow of 1.50 L/min, the read time was 60 s, and the nebulizer pressure was 250 kPa. Operating optimal parameters were: radio-frequency generator (1400 W). Sample uptake time, rinse time, initial stabilization time was 240 total, 45 and pre-flush 45 s, respectively, delay time and time between replicate analysis were zero. Type of detector solid state and spray chamber was CCD and Cyclonic, Modified Lichte, respectively. Prewash pump speed (rpm) was 60 (for 15 s) and 30 (for 30 s) and Prewash time was 45 s; at the end, sample injection pump speed was 30 rpm (Fathabad et al., 2018; Taghizadeh et al., 2017; Zhu et al., 2011).

2.5. Extraction procedures

2.5.1. Concentrations of pesticides

The method used by Qin et al. (2016) was applied with slight modifications. For this purpose, 2.5 g of each sample was placed in a 50-mL falcon tube, and then mixed with 5 µL/mL of internal standard



Fig. 1. Cultivation zones where date fruits were collected.

Table 1

Operating program used for microwave digestion.

Power (W)	Time (min)	Final Temperature (°C)	Initial Temperature (°C)	Phase
1	25	90	5	700
2	90	90	3	600
3	90	170	10	600
4	170	170	7	600

triphenylmethane in EtOAc. The solution was incubated for 1 h in a cold and dark room. Then, 5 mL deionized distilled water was added and the solution was vigorously stirred during one min. Next, 10 mL MeCN and 5 mL n-hexane were added and shaken well. A mixture of 4 g MgSO₄ and 1 g NaCl was added to the tube and the tube was shaken for 3 min. The mixture was centrifuged at 4000 g for 10 min at -5 °C. Afterwards, 5 mL of the supernatant was transferred to a 15-mL falcon containing sorbents (i.e. 0.4 g of C18, 0.2 g of Primary and Secondary Amine (PSA) and 1 g of magnesium sulfate). The prepared solution was stirred for 2 min then, centrifuged at 4000 g for 10 min at -5 °C, and 4 mL of the supernatant was transferred to a 5-mL flask. The samples were concentrated under a nitrogen atmosphere to 0.3–0.5 mL, then reconstituted to 1 mL using toluene and stirred for 3 min. Eventually, 2 µL of the final solution was injected into the GC–MS. Acetonitrile and magnesium sulfate dehydrate salt were used for extraction of the analytes. PSA and C18 were also used to remove non-polar substances such as lipids to prevent interference. To eliminate the matrix effects, analysis of spiked samples was done, and then the concentrations of pesticides were calculated by interpolation of the relative peak areas for each pesticide to internal standard peak area in the sample, on the spiked calibration curve (Bernardi et al., 2016; Chen et al., 2013; Gilbert-López et al., 2010; Qin et al., 2016b).

2.5.2. Metals

For metals analysis, 10 g of each sample was digested using 60 mL of HNO₃ and 20 mL of concentrated H₂O₂ (30 %) by using microwave digestion system (Milestone Ethos Microsynth Oven, Germany) for 25 min and then, diluted to 100 mL using 2 % HNO₃. Blank preparation was done in the same way. Finally, clear liquid samples were analyzed by ICP-OES (Ciarkowska et al., 2019).

2.5.3. PAHs

Briefly, 2 g of each sample was added to 10 mL acetonitrile/hexane (60:40 v/v) and shaken for 1 min. The mixture was ultra-sounded for 5 min at 60 °C. The homogenized solution was centrifuged at 4000 g for 5 min and then the top layer was removed. The remaining oil was mixed with 10 mL acetonitrile/hexane. The solution with PAHs was passed through a C₁₈ cartridge and evaporated under nitrogen at 35 °C. Consequently, in the second phase of purification, the solution was purified using Florisil cartridge (500 mg) as follows: 1 mL sample from the previous step was added to the cartridge, and mixed with 4 mL hexane/dichloromethane (75:25 v/v). Reducing volume to 50 µL was completed under nitrogen at 35 °C. Using a microliter syringe loaded with tetrahydrofuran/methanol (50:50 v/v), the final volume was adjusted to 250 µL (Gilbert-López et al., 2010; Surma et al., 2014; Sztternfeld et al., 2019; Yousefi et al., 2018).

2.6. Analytical performance

Method validation was performed based on European Union (EU) guidelines SANTE 12682/ 2019, IMEP 114 and PAHs Factsheet for pesticides, metals and PAHs (EU, 2019; Lerda, 2011; SANTE, 2019; Taghizadeh et al., 2017).

2.6.1. Pesticides

The stock solution of triphenylmethane used as the internal standard (1 mg/mL), was prepared in EtOAc and kept in glass vials in a dark place at -20 °C. For recovery experiments, a standard mixture solution of pesticides (10 µg/mL) was prepared in EtOAc. Each pesticide and pesticide mixture (including all 22 pesticides) were injected to GC–MS individually. The calibration curve for each pesticide was plotted by calculating the ratio of the peak area of standards to peak area of internal standard, against the concentration. Limit of detection (LOD) was determined by considering a signal-to-noise ratio of 3 with reference to the background noise obtained from blank sample, whereas limit of quantification (LOQ) was determined by considering a signal-to-noise

ratio of 10 irrespective of the matrices by using matrix-matched standards (Feng et al., 2020; Taghizadeh et al., 2020c).

2.6.2. Metals

For the quantitative analysis of metals in samples, multi-element (As, Cd, Cr, Hg, Ni, and Pb) standard solution at 1000 mg/L, was prepared for plotting calibration curves. Stock solution was diluted with 0.2 % HNO₃ solution. For recovery determination, spiked samples were prepared in triplicates and then, treated according to the procedure described in sample preparation. The recoveries were calculated using the spiked calibration curves (Taghizadeh et al., 2020b).

2.6.3. PAHs

Stock solution of PAHs at 1000 mg/L was prepared in n-hexane and wrapped in aluminum foil. Triphenyl phosphate stock solution was provided in acetone at 1000 mg/L. All the stocks were kept in a dark place at -20 °C. Quality assurance and quality control were ensured by quantification of recoveries from matrix spikes. Compounds quantification was performed by using an internal standard method. The calibration curve for each compound was constructed by plotting the ratio of the peak area of standards to peak area of internal standard against the concentration. LOD (defined as signal to-noise 3:1) and LOQ (defined as signal to-noise 10:1) were also calculated. Method precision was analyzed by intra-day and inter-day (for three concentrations on each day, for three consecutive days) assays (Lee et al., 2019; Lerda, 2011; Moudgil et al., 2019).

2.7. Relative potency factor (RPF)

Based on the EFSA (EFSA, 2012) and USEPA (USEPA, 2011b) recommendations, the Relative Potency Factor (RPF) was used in cumulative the risk assessment method. Estimated exposures of each compound were recommended by EFSA to be normalized in relation to Index Compounds (IC-normalized values) (De Rop et al., 2019). In the current study, RPFs for organophosphorus (OPs) and carbamates (CBs) were taken from the USEPA, which were calculated by Bench Mark Doses (BMD₁₀) related with a 10 % rat brain AChE (acetylcholinesterase) inhibition using methamidophos or acephate for OPs and oxamyl for CBs as IC. We also used deltamethrin as IC for pyrethroids (USEPA, 2006, 2011a). If BMD₁₀ (for OPs and CBs) and/or BMD₂₀ (for PYs) were not available, No Observed Adverse Effect Level (NOAEL) from rats, dogs or humans primarily published by EFSA, and from European Commission (EC), FAO/WHO Joint Meeting on Pesticide Levels (JMPPR) and USEPA, were estimated (Jardim et al., 2018). Table 8 shows the RPFs for the pesticides of different classes found in date fruits.

2.8. Toxic equivalency factor (TEF)

The Toxic Equivalency Factor (TEF) is used to calculate toxic equivalent concentrations of matrix PHAs. The carcinogenic potency of PAHs was calculated relative to that of BaP as a reference compound (Jiang et al., 2016). Table 10 shows the TEFs for the PAHs used in this study.

2.9. Health risk assessment

2.9.1. Non- carcinogenic scenario

Chronic daily intake (CDI) (mg/kg body mass (BM)) using in date palm fruit, was determined Eq. 1. The Hazard Quotient (HQ) was calculated by using the Eq. 2). ADIs values set by various jurisdictions and agencies for the 22 pesticides and 8 metals considered in the present work, are presented in Tables 8 and 9, respectively (Singh and Agarwal, 2018; Taghizadeh et al., 2019b).

$$\text{CDI (Chronic Daily Intake)} = \frac{\text{CF} \times \text{IR} \times \text{EF} \times \text{ED}}{\text{BM} \times \text{AT}} \quad (1)$$

CF: Contaminant concentration in date fruits (mg/kg, dry mass (dm))

IR: Ingestion rate, the daily date consumption (kg).

The value of consumption used in the current study is 21.91 g/person/day for date for Iranian general population. These values correspond to the average consumption based on tonnages of production and country population (FAO, 2020).

EF: Exposure frequency (365 meals/year)

ED: Exposure duration (70 years) (Taghizadeh et al., 2018).

BM: Average body mass for Iranian adult population is considered 70 kg (Taghizadeh et al., 2020a).

AT: Average time (25550 days or 70 years)

$$HQ = \frac{CDI}{ADI} \quad (2)$$

The Hazard Index (HI) was used to estimate the total risk from non-carcinogenic effects posed by the chemical mixture. The HI of chemical mixture was calculated by Eq. 3. The USEPA states that if $HI < 1.0$, there is no appreciable risk of adverse health effects while $HI < 1.0$ indicates a chance for non-cancer effects (USEPA, 2009).

$$HI = \sum_{n=0}^i HQ_n \quad (3)$$

2.9.2. Carcinogenic scenario

Carcinogenic risk was evaluated based on Incremental Life Time Cancer Risk (ILCR) of intake of carcinogenic elements present in samples (Eq. 4). It was conducted using CDI, Cancer Slope Factor of BaP (CSF) (geometric mean of 7.3 mg/kg, BM/day) and CF is the conversion factor (10^{-6} mg/ng) (Ni and Guo, 2013; USEPA, 2004). For ILCR, the values ranging from 10^{-6} to 10^{-4} imply risk, whereas the values $>10^{-4}$ indicate greater risks (JECFA, 2006; Singh and Agarwal, 2018).

$$ILCR = CDI \times CSF \times CF \quad (4)$$

Recently, EFSA has applied another concept to the genotoxic carcinogen risk assessment. Margins of Exposure (MoE) compares the actual mean or maximum exposure in humans with the point of departure (POD) for example BMDL₁₀ (Bench Mark Dose with 10 % effect) from a cancer experiment in animals. BMDL₁₀ is the bench mark dose of the lower confidence limit to increase the amount of animals bearing tumor by 10 %. BMDL₁₀ and CDI should have the dimension of a dose (mg/kg body mass (BM)), producing a dimensionless MoE (Eq. 5). EFSA suggested that an MoE $<10,000$ indicates 'de minimis public health concern' while MoEs $\leq 10,000$ imply 'of concern' (Lee et al., 2018; Taghizadeh et al., 2019c).

$$MoE = (BMDL_{10}/CDI) \quad (5)$$

Where BMDL₁₀ is equal to 0.49 mg/kg, BM/day for PAHs (carcinogenic PAHs) (EFSA 2010a). EFSA has so far mainly used substitution methods, i.e. for results reported to be below the Limit of Detection (LOD), the value was imputed as the LOD (upper bound), as zero (lower bound) or LOD/2 (medium or middle bound) (EFSA, 2010b). In this study, we used the middle bound.

2.10. Uncertainty and sensitivity analyses- Monte Carlo simulation

In HRA, the frequency and degree of uncertainties can be affected by insufficient data, various parameters, and the type of the model used. During the 1980s, the USEPA recognized Monte Carlo (MC) to determine the uncertainties in HRA for chemical mixtures (Dong et al., 2015). MC method provides a clear view of the distribution of uncertainties (Uusitalo et al., 2015).

The MC simulation with 10,000 iterations was considered for evaluation of carcinogenic and non-carcinogenic health risk for oral intake of pesticide, metals, and PAHs present in date fruits. The sensitivity analysis illustrates the influence of the carcinogenic and non-carcinogenic health risk variables (Kaur et al., 2020). In current

calculations, distribution mode was chosen as "log-normal" by SAS software JMP 8 (Campus Drive, Cary, NC 27513).

2.11. Statistical analysis

Statistical analysis was performed by SAS software JMP 8 (Campus Drive, Cary, NC 27513). Significant differences among mean values were determined by using LSD at a probability of 0.05. The uncertainty and sensitivity analyses were all implemented by SAS software JMP 8 (Campus Drive, Cary, NC 27513).

3. Results

3.1. Analytical performance for pesticides

As shown in Table 2, three matrices were spiked at three concentrations (10, 20, and 50 µg/kg) with 22 standard pesticides. The results showed that most of the average recovery percentages were in the range of 94.1–99.5 %. The Relative Standard Deviations (RSDs %) were ≤ 6.5 %. Analytical performance results were in accordance with those reported by European Union guidelines SANTE 12682/ 2019 and reflecting successful validation and good method performance (EU, 2019). Coefficients of determination (R^2) were calculated for each pesticide using its calibration plot; R^2 ranged 99.4–100 % (Table 2).

Also, LODs and LOQs were calculated on the basis of signal-to-noise ratios of 3 and 10, respectively. Based on our results, the LODs ranged 0.1–3.2 µg/kg and LOQs ranged 0.3–9.3 µg/kg (Table 2).

3.2. Analytical performance for metals

Recoveries from date matrices were determined at three concentrations. Recoveries were in the range of 91.2–100 %, with an associated RSD of ≤ 4.2 %. The obtained recoveries confirmed the appropriateness of extraction with no significant loss of metals. Coefficients of determination (R^2) exhibited significant linear relationships (99.2–99.9 %) for all the calibration curves (Table 3). LODs and LOQs were similar for all metals (1.0 and 3.0 µg/kg, dm, respectively) with the exception of Ni (7.0 and 21.0 µg/kg, dm, respectively).

3.3. Analytical performance for PAHs

Satisfactory recoveries were observed for PAH4 (Table 4). Mean percentages of recovery ranged from 90.0–100 %, with an associated RSD ≤ 7.5 %. Analytical curves for PAH4 presented appropriate R^2 values that ranged 99.4–99.9 %. The LODs were 0.15–1.0 µg/kg and LOQs were 0.45–3.0 µg/kg (Table 4).

3.4. Concentrations of contaminants

3.4.1. Concentrations of pesticides

Mean concentrations of pesticides in 900 samples analyzed in the present work, are shown in Table 5. The OPs, CBs, and PYs levels did not show statistically significant variations among date cultivars. Also, the 6 cultivation zones were not significantly different in terms of pesticides levels ($P = 0.7-0.99$) (Table 5).

3.4.2. Concentrations of metals

Concentrations of metals in 900 samples analyzed in the present work are shown in Table 6. Mean concentrations of metals statistically differed among the six cultivation zones (Table 6).

3.4.3. Concentrations of PAHs

Mean concentrations of PAHs in collected samples are given in Table 7. Concentrations of PAHs in samples did not significantly vary among the cultivars ($p < 0.05$). Also, concentrations of PAHs did not vary significantly among the cultivation zones (Table 7).

Table 2

Mean recoveries, relative standard deviation (RSD, %) of 22 pesticides at three spiked concentrations ($\mu\text{g}/\text{kg}$, dry mass (dm)), correlation coefficients (R²), limit of detection (LOD) and limit of quantification (LOQ) ($\mu\text{g}/\text{kg}$, dry mass (dm)) of pesticides.

Pesticide	spiked concentration			R ²	LOD ^d	LOQ ^e
	10 $\mu\text{g}/\text{kg}$	20 $\mu\text{g}/\text{kg}$	50 $\mu\text{g}/\text{kg}$			
OP ^a pesticides						
Acephate	95.1 (2.4)	96.2 (3.3)	99.1 (5.4)	0.999	2.0	6.0
Azinphos-methyl	94.1 (3.1)	95.1 (4.2)	98.3 (5.3)	0.994	3.1	9.3
Chlorpyrifos	96.2 (3.0)	97.5 (5.5)	99.2 (6.1)	0.995	0.1	0.3
Chlorpyrifos-methyl	96.5 (3.0)	97.5 (4.3)	98.5 (5.0)	0.998	0.1	0.3
Diazinon	97.5 (2.5)	98.3 (3.2)	99.3 (4.5)	0.999	0.9	1.9
Dimethoate	96.0 (4.1)	97.5 (5.1)	99.2 (5.5)	0.999	3.0	9.0
Ethion	95.3 (3.4)	98.0 (3.3)	99.3 (4.1)	0.999	2.0	6.0
Fenitrothion	95.1 (3.2)	97.4 (5.5)	99.0 (6.4)	0.997	0.1	0.3
Fenthion	97.1 (2.3)	98.5 (3.4)	99.3 (5.2)	1.000	0.1	0.3
Malathion	95.2 (3.3)	97.1 (4.1)	99.0 (6.3)	1.000	3.2	9.1
Methamidophos	94.5 (4.2)	96.3 (4.5)	98.5 (5.2)	0.999	3.0	9.1
Methidathion	95.1 (5.1)	97.3 (3.5)	98.5 (4.5)	0.999	3.1	9.1
Phenthoate	96.5 (4.5)	97.5 (5.2)	99.4 (4.2)	0.998	3.0	9.2
Trichlorfon	96.5 (3.3)	98.1 (4.1)	99.5 (6.3)	0.995	3.0	9.1
CB ^b pesticides						
Carbaryl	96.1 (4.5)	97.2 (5.5)	99.5 (6.3)	0.999	3.2	9.3
Carbofuran	96.2 (3.5)	98.1 (4.2)	99.4 (4.5)	0.999	0.1	0.5
Methomyl	97.1 (4.3)	98.5 (5.1)	99.5 (6.1)	1.000	0.2	0.6
Oxamyl	95.1 (4.1)	97.5 (4.5)	99.5 (6.5)	0.997	2.0	6.0
Pirimicarb	96.5 (4.4)	98.0 (3.3)	99.2 (5.2)	0.996	3.0	9.0
Propamocarb	97.0 (3.2)	98.5 (4.2)	99.4 (6.5)	0.999	3.0	9.0
PY ^c pesticides						
Deltamethrin	96.1 (3.3)	98.2 (3.5)	99.4 (5.3)	0.999	2.0	6.0
Permethrin	95.5 (4.5)	97.4 (4.1)	98.5 (6.1)	0.999	3.0	9.0

^a Organophosphorus.

^b Carbamate.

^c Pyrethroid.

^d Limit of Detection.

^e Limit of Quantitation.

3.5. Assessments of risk

3.5.1. HRA for pesticides

Table 8 shows the 50th and 95th percentiles of HQs and HIs calculated in non-carcinogenic risk scenario. Based on the MCS, HI (50%) for OP group of pesticides in date samples was 4.61×10^{-3} . At the 95th percentile, the total HI value were <1.0 (8.64×10^{-3}). At the 50th percentile, in CBs, HI (50th percentile) was 1.43×10^{-3} , and at the 95th percentile, it was 2.24×10^{-3} . The 50th percentile of HIs for PYs was 3.00×10^{-5} , but at 95th, it was 8.10×10^{-5} . Similarly, total HI values were below one at both percentiles (Table 8).

Table 3

Mean recoveries, Relative Standard Deviation (RSD, %) and coefficients of determination (R²) for six metals at three spiked concentrations ($\mu\text{g}/\text{kg}$, dry mass (dm)).

Metal	Date			R ²
	50 $\mu\text{g}/\text{kg}$	100 $\mu\text{g}/\text{kg}$	150 $\mu\text{g}/\text{kg}$	
As	93.5 (2.4)	100 (1.1)	97.1 (2.1)	0.999
Cd	93.5 (2.0)	99.5 (1.2)	97.4 (3.5)	0.999
Cr	91.2 (3.1)	99.4 (1.3)	99.1 (1.3)	0.999
Hg	94.4 (3.1)	98.2 (2.4)	99.3 (4.2)	0.992
Ni	95.3 (1.5)	99.3 (1.5)	97.5 (2.0)	0.999
Pb	96.1 (2.2)	99.5 (2.0)	98.2 (3.3)	0.999

Table 4

Mean recoveries, relative standard deviation (RSD, %) of 16 PAHs ($\mu\text{g}/\text{kg}$, dry mass (dm)), correlation coefficients (R²), limit of detection (LOD) and limit of quantification (LOQ) ($\mu\text{g}/\text{kg}$, dry mass (dm)) of PAHs.

PAHs ^a	Date			R ²	LOD ^b	LOQ ^c
	5 $\mu\text{g}/\text{kg}$	10 $\mu\text{g}/\text{kg}$	20 $\mu\text{g}/\text{kg}$			
Acenaphthene (Ace)	91.1 (5.4)	95.1 (3.1)	99.8 (5.3)	0.999	0.25	0.60
Acenaphthylene (Acy)	93.4 (5.2)	100 (4.3)	96.1 (6.4)	0.999	0.25	0.70
Anthracene (Ant)	95.0 (5.0)	100 (3.3)	97.5 (6.3)	0.999	0.30	0.90
Benzo[a]Anthracene (BaA)	94.1 (4.8)	100 (5.4)	98.2 (7.5)	0.999	0.20	0.60
Benzo(a)Pyrene (BaP)	95.4 (6.4)	100 (4.4)	97.2 (2.0)	0.999	1.00	3.00
Benzo[b]Fluoranthene (BbF)	93.4 (7.0)	99.9 (5.4)	96.3 (7.4)	0.999	0.20	0.60
Benzo[g,h,i]Perylene (BghiP)	94.2 (6.3)	98.4 (5.4)	100 (5.0)	0.998	0.25	0.70
Benzo[k]Fluoranthene (BkF)	95.0 (5.1)	98.3 (5.4)	100 (7.5)	0.995	0.25	0.70
Chrysene (Chr)	96.4 (6.0)	97.5 (4.4)	99.5 (4.4)	0.999	0.15	0.50
Dibenzo[a,h]anthracene (DahA)	95.4 (7.1)	98.3 (2.5)	96.3 (6.4)	0.999	0.25	0.70
Fluorene (Fl)	91.4 (4.4)	97.0 (5.0)	99.5 (3.1)	0.994	0.15	0.45
Fluoranthene (Flu)	92.5 (6.4)	96.3 (3.5)	99.4 (5.2)	0.995	0.15	0.50
Indeno[1,2,3-cd]pyrene (IcdP)	96.1 (5.5)	99.1 (3.3)	100 (3.2)	0.995	0.25	0.60
Naphthalene (Nap)	90.3 (7.4)	95.3 (4.0)	100 (6.5)	0.995	0.15	0.45
Phenanthrene (Phe)	91.4 (4.2)	94.2 (4.1)	99.4 (7.0)	0.995	0.15	0.45
Pyrene (Pyr)	90.0 (6.4)	98.0 (5.4)	100 (5.3)	0.997	0.30	1.00

^a Polycyclic Aromatic Hydrocarbons.

^b Limit of Detection.

^c Limit of Quantitation.

3.5.2. HRA for metals

Estimated exposure percentiles to carcinogenic and non-carcinogenic metals are given in Table 9. For the carcinogenic metals estimated ILCRs at the 50th and 95th percentiles in date palm fruit were 2.25×10^{-7} and 7.10×10^{-7} respectively for AS, and 1.24×10^{-9} and 5.38×10^{-9} respectively for Pb. For non-carcinogenic metals, estimated HQs at the 50th and 95th percentiles of risks posed by consumption of date fruit ranged from 3.00×10^{-5} to 1.50×10^{-3} , and 6.25×10^{-5} to 4.20×10^{-3} , respectively. HI values were less than 1.0 at both percentiles for all samples (Table 9).

3.5.3. HRA for PAHs

The percentiles of estimated ILCRs and MoEs of 16 PAHs in three matrices are reported in Table 10. At the 50th and 95th percentiles, the

Table 5
Mean concentrations ($\mu\text{g}/\text{kg}$, dry mass (dm)) \pm SD of organophosphorus, carbamate, and pyrethroid plotted for each cultivar and each zone.

Pesticide	Cultivar												Zone			
	Barhi	Deri	Estamaran	Kabkab	Mazafati	Medjool	Piarom	Rabbi	Shahani	Zahedi	Abadan	Bam	Dashtestan	Jahrom	Minab	Saravan
OP ^a pesticides																
Acephate	<LOD ^d	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Azinphos-methyl	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Chlorpyrifos	1.79 \pm 0.10	1.74 \pm 0.21	1.67 \pm 0.35	1.63 \pm 0.23	1.86 \pm 0.11	1.72 \pm 0.12	1.56 \pm 0.30	1.55 \pm 0.15	1.76 \pm 0.10	1.49 \pm 0.11	1.14 \pm 0.15	1.59 \pm 0.22	1.84 \pm 0.13	1.89 \pm 0.31	1.79 \pm 0.12	1.81 \pm 0.14
Chlorpyrifos-methyl	1.28 \pm 0.15	1.57 \pm 0.10	1.44 \pm 0.12	1.33 \pm 0.11	1.69 \pm 0.21	1.16 \pm 0.10	0.99 \pm 0.11	1.01 \pm 0.21	1.20 \pm 0.10	0.77 \pm 0.05	1.26 \pm 0.11	2.00 \pm 0.10	0.66 \pm 0.13	1.23 \pm 0.21	1.15 \pm 0.10	1.17 \pm 0.11
Diazinon	2.52 \pm 0.34	2.37 \pm 0.21	2.28 \pm 0.10	1.79 \pm 0.15	3.33 \pm 0.13	2.37 \pm 0.31	1.94 \pm 0.21	2.04 \pm 0.11	3.26 \pm 0.41	1.92 \pm 0.25	2.63 \pm 0.44	2.16 \pm 0.10	2.37 \pm 0.30	2.35 \pm 0.31	2.56 \pm 0.20	2.20 \pm 0.12
Dimethoate	9.91 \pm 0.35	9.92 \pm 0.51	9.82 \pm 0.41	9.92 \pm 0.35	10.06 \pm 1.11	9.72 \pm 0.51	9.73 \pm 0.50	10.02 \pm 1.41	9.42 \pm 0.82	9.79 \pm 1.10	10.08 \pm 1.11	9.77 \pm 1.10	9.95 \pm 1.14	10.02 \pm 1.55	9.53 \pm 2.00	9.62 \pm 1.41
Ethion	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Fenitrothion	1.50 \pm 0.15	1.42 \pm 0.10	1.36 \pm 0.11	1.35 \pm 0.11	1.42 \pm 0.10	1.38 \pm 0.14	1.16 \pm 0.21	1.09 \pm 0.10	1.62 \pm 0.12	1.08 \pm 0.10	1.81 \pm 0.10	1.80 \pm 0.10	0.73 \pm 0.04	0.73 \pm 0.03	1.15 \pm 0.10	1.30 \pm 0.94
Fenthion	LOQ ^e	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ
Malathion	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methamidophos	10.00 \pm 2.01	9.76 \pm 1.22	9.61 \pm 1.82	9.77 \pm 1.31	10.15 \pm 1.05	9.85 \pm 1.33	9.82 \pm 1.50	9.89 \pm 2.42	9.73 \pm 1.85	9.68 \pm 2.10	9.73 \pm 2.41	10.45 \pm 1.61	9.80 \pm 2.34	9.78 \pm 1.74	9.53 \pm 1.32	9.66 \pm 1.70
Methidathion	9.99 \pm 1.70	9.86 \pm 1.34	9.87 \pm 1.15	10.18 \pm 2.00	10.32 \pm 0.11	9.88 \pm 1.43	9.64 \pm 1.80	9.79 \pm 1.91	9.74 \pm 1.13	9.50 \pm 1.33	11.12 \pm 1.15	9.54 \pm 0.81	9.70 \pm 1.44	9.68 \pm 1.50	9.96 \pm 1.35	9.16 \pm 1.81
Phenthoate	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trichlorfon	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
CB ^b pesticides																
Carbaryl	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ
Carbofuran	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methomyl	1.36 \pm 0.09	1.48 \pm 0.10	1.50 \pm 0.15	1.52 \pm 0.14	1.39 \pm 0.07	1.55 \pm 0.08	1.49 \pm 0.09	1.47 \pm 0.09	1.47 \pm 0.09	1.33 \pm 0.08	0.98 \pm 0.05	1.56 \pm 0.04	1.43 \pm 0.10	1.75 \pm 0.11	1.60 \pm 0.09	1.41 \pm 0.10
Oxamyl	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ
Pirimicarb	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Propamocarb	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
PY ^c pesticides																
Deltamethrin	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Permethrin	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

^a Organophosphorus.

^b Carbamate.

^c Pyrethroid.

^d Limit of Detection.

^e Limit of Quantitation.

Table 6
Mean concentrations ($\mu\text{g}/\text{kg}$, dry mass (dm)) \pm SD of metals plotted for each cultivar and each zone.

Metal	Cultivar										Zone					
	Barhi	Deri	Estamaran	Kabkab	Mazafati	Medjool	Piarom	Rabbi	Shahani	Zahedi	Abadan	Bam	Dashtestan	Jahrom	Mimab	Saravan
As	<LOD ^a	<LOD														
Cd	3.59 \pm 0.13	3.59 \pm 0.15	3.60 \pm 0.10	3.69 \pm 0.11	3.57 \pm 0.12	3.70 \pm 0.14	3.63 \pm 0.10	3.69 \pm 0.22	3.85 \pm 0.12	3.79 \pm 0.20	3.44 \pm 0.13	3.58 \pm 0.12	4.27 \pm 0.23	3.41 \pm 0.14	3.54 \pm 0.20	3.78 \pm 0.15
Cr	3.41 \pm 0.21	3.47 \pm 0.31	3.49 \pm 0.11	3.54 \pm 0.14	3.42 \pm 0.24	3.53 \pm 0.15	3.38 \pm 0.22	3.44 \pm 0.12	3.55 \pm 0.14	3.54 \pm 0.10	3.35 \pm 0.11	3.57 \pm 0.20	3.38 \pm 0.21	3.61 \pm 0.10	3.28 \pm 0.11	3.66 \pm 0.10
Hg	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ni	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Pb	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

^a Limit of Detection.

ILCR was 5.39×10^{-12} and 8.76×10^{-12} , respectively. Based on the MCS model, the 50th and 95th percentile values for MoE were 1.16×10^{11} and 2.97×10^{11} , respectively (Table 10).

3.6. Sensitivity analysis

Based on the MCS sensitivity analysis of HQ, ILCR, and MoE data, concentration (0.52 %) was the most significantly influential variable for exposure to pesticides in date fruit, while body mass contributed the least (-18.4 %) (Fig. 2). Also, concentration was the key input parameter for exposure to metals. Considering the carcinogenic scenario for metals, influence of concentration was approximately 12.27 %. In ILCR, concentration was the most significantly influential parameter while in MoE, body mass had the greatest effect (Fig. 2).

4. Discussion

Contamination of fruits raises health concerns as they are usually consumed raw or semi-processed. Mean concentrations of pesticides in date samples analyzed in the present work, did not show statistically significant variations among date cultivars and cultivation zones. Different geographical zones were expected to represent different pesticide application patterns (from different incidence of pests and edaphic conditions (factors with great impact on pesticide persistence in crops). However, in the current study, no significant differences were found in the total pesticide content among the zones. As information of pesticide application is not available for the water irrigation and soils sampling points, and as other factors might have affected the pesticide results by zones (e.g. different number of soil samples selected per crop system, different climate and soil conditions), no clear conclusions can be drawn between the diversity of products and pesticide use in the different zones and the occurrence and measured content of pesticide residues in date fruits. Another reason to believe that our results could be extrapolated for the current situation is the fact that none of the most relevant pesticides of this study (in terms of frequency and concentration in date) was banned from Iranian markets since the sampling time. In addition, the ones that had their approval extended in the meantime kept the same recommended applications rates. Of course, some very recently approved substances might have replaced some of older approved ones but, as the use of individual active substances is not available in Iranian databases, it would be too speculative to assume significant changes in the pesticide products used by Iranian farmers in such a short period of time (Silva et al., 2019).

In this work, combined exposure to OPs, CBs, and PYs which exert common modes of action (Hassani et al., 2015; Li et al., 2016) was considered to estimate HI. The results of this study indicated an HI < 1 for simultaneous oral exposure to 22 pesticides, revealing no major risk. All concentrations of pesticides were less than Maximum Residue Limits (MRLs); set by EU legislations (Table 8). Consistently, evaluation of PYs concentrations in 1450 fruit samples from China, showed that consumers were not at risk due to long-term ingestion of the fruits; however, in acute cumulative exposure to PYs, HI values exceeded 1.0 in 0.76 % of samples (Li et al., 2016). In another study performed in China, it was found that a small proportion of fruits and vegetables samples contained pesticides at concentrations greater than their MRLs; Of 1135 samples (37.7 %) that contained pesticide residues, pakchoi cabbage, legumes, and leaf mustard were most frequently detected with pesticide residues, with 17.2, 18.9 and 17.2 % of the samples exceeding the MRLs, respectively. Concerning the most frequently detected pesticide residues, cypermethrin was found in 18.7 % of the samples analyzed (Chen et al., 2011). According to the findings of a study on grape, peach, pear, and apple samples in Spain, λ -cyhalothrin and cypermethrin were the most frequently detected pesticides. Of 752 samples analyzed, 336 samples (45 %) had levels above the LOQ for all analyzed pesticides; however, in only 13 (3 %) out of the 336 samples, pesticides levels

Table 7
Mean concentrations ($\mu\text{g}/\text{kg}$, dry mass (dm)) \pm SD of Polycyclic Aromatic Hydrocarbons (PAHs) plotted for each cultivar and each zone.

PAHs ^a	Cultivar										Zone					
	Barhi	Deri	Estamaran	Kabkab	Mazafati	Medjool	Piarom	Rabbi	Shahani	Zahedi	Abadan	Bam	Dashtestan	Jahrom	Minab	Saravan
Acc ^b	<LOD ^r	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD									
Acy ^c	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ant ^d	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BaA ^e	0.38 \pm 0.03	0.41 \pm 0.04	0.40 \pm 0.02	0.42 \pm 0.03	0.43 \pm 0.04	0.38 \pm 0.04	0.38 \pm 0.05	0.37 \pm 0.02	0.37 \pm 0.04	0.39 \pm 0.05	0.76 \pm 0.05	<LOD	0.30 \pm 0.04	<LOD	0.82 \pm 0.03	LOQ ^s
BaP ^f	1.75 \pm 0.11	2.50 \pm 0.23	2.29 \pm 0.12	2.33 \pm 0.11	2.46 \pm 0.15	2.34 \pm 0.11	2.34 \pm 0.13	2.32 \pm 0.32	2.52 \pm 0.11	2.16 \pm 0.14	3.13 \pm 0.12	<LOD	4.34 \pm 0.30	3.23 \pm 0.22	LOQ	LOQ
BbF ^g	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BghiP ^h	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BkF ⁱ	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Chr ^j	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ
DaHA ^k	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Fl ^l	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flu ^m	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
IcdP ⁿ	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nap ^o	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phen ^p	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ	LOQ
Pyr ^q	1.15 \pm 0.30	1.04 \pm 0.20	1.10 \pm 0.13	1.15 \pm 0.22	1.14 \pm 0.10	1.12 \pm 0.11	1.08 \pm 0.33	1.15 \pm 0.21	1.25 \pm 0.14	1.19 \pm 0.25	1.24 \pm 0.15	<LOD	1.24 \pm 0.13	1.19 \pm 0.21	1.30 \pm 0.24	1.27 \pm 0.20

^a Polycyclic aromatic hydrocarbons.

^b Acenaphthene.

^c Acenaphthylene.

^d Anthracene.

^e Benzo[a]Anthracene.

^f Benzo(a)Pyrene.

^g Benzo[b]Fluoranthene.

^h Benzo[g,h,i] Perylene.

ⁱ Benzo[k]Fluoranthene.

^j Chrysene.

^k Dibenzo[a,h]anthracene.

^l Fluorene.

^m Fluoranthene.

ⁿ Indeno[1,2,3-cd]pyrene.

^o Naphthalene.

^p Phenanthrene.

^q Pyrene.

^r Limit of Detection.

^s Limit of Quantitation.

Table 8

Estimated exposure percentiles for organophosphorus pesticides (OPs); carbamates (CBs) and pyrethroids (PYs).

Pesticide	European union		Reference	RPF ^a	HQ ^b	
	ADI ^c	MRL ^d			50 %	95 %
OP pesticide		Date		IC ^f = Methamidophos		
Acephate	0.03	0.01	Reg. (EU) No 899/2012	0.08	8.00×10^{-7}	1.00×10^{-6}
Azinphos-methyl	0.005	0.05	Reg. (EU) No 839/2008	0.1	9.30×10^{-6}	1.00×10^{-5}
Chlorpyrifos	0.001	0.01	Reg. (EU) No 686/2018	0.06	3.00×10^{-5}	8.00×10^{-5}
Chlorpyrifos-methyl	0.01	0.01	Reg. (EU) No 686/2018	0.005	1.87×10^{-7}	6.87×10^{-7}
Diazinon	0.0002	0.01	Reg. (EU) No 834/2013	0.01	3.57×10^{-5}	7.30×10^{-5}
Dimethoate	0.002	0.01	Reg. (EU) No 1135/2017	0.32	4.70×10^{-4}	9.70×10^{-4}
Ethion	0.002	0.01	Reg. (EU) No 310/2011	1	1.50×10^{-4}	6.50×10^{-4}
Fenitrothion	0.005	0.01	Reg. (EU) No 8990/2012	0.083	6.68×10^{-6}	1.07×10^{-5}
Fenthion	0.007	0.01	Reg. (EU) No 310/2011	0.33	2.12×10^{-6}	6.10×10^{-6}
Malathion	0.03	0.02	Reg. (EU) No 399/2015	0.00	0	0
Methamidophos	0.001	0.01	Reg. (EU) No 899/2012	1	2.90×10^{-3}	5.70×10^{-3}
Methidathion	0.001	0.02	Reg. (EU) No 310/2011	0.32	9.47×10^{-4}	1.10×10^{-3}
Phenthoate	0.003	–	Reg. (EU) No 839/2008	0.1	1.50×10^{-5}	4.30×10^{-5}
Trichlorfon	0.002	0.02	Reg. (EU) No 899/2012	0.003	6.75×10^{-7}	1.30×10^{-6}
Hazard Index (HI)					4.61×10^{-3}	8.64×10^{-3}
CB pesticide				IC= Oxamyl		
Carbaryl	0.008	0.01	Reg. (EU) No 1096/2014	0.15	2.98×10^{-5}	8.20×10^{-5}
Carbofuran	0.00015	0.003	Reg. (EU) No 399/2015	2.4	3.60×10^{-4}	6.90×10^{-4}
Methomyl	0.0025	0.01	Reg. (EU) No 1822/2016	0.67	1.46×10^{-4}	4.70×10^{-4}
Oxamyl	0.001	0.01	Reg. (EU) No 552/2019	1	9.00×10^{-4}	1.00×10^{-3}
Pirimicarb	0.02	0.01	Reg. (EU) No 71/2016	0.02	2.57×10^{-7}	5.57×10^{-7}
Propamocarb	0.4	0.01	Reg. (EU) No 832/2018	0.00	0	0
Hazard Index (HI)					1.43×10^{-3}	2.24×10^{-3}
PY pesticide				IC= Deltamethrin		
Deltamethrin	0.01	0.01	Reg. (EU) No 832/2018	1	3.00×10^{-5}	8.00×10^{-5}
Permethrin	0.05	0.05	Reg. (EU) No 623/2017	0.09	8.00×10^{-5}	1.00×10^{-6}
Hazard Index (HI)					3.00×10^{-5}	8.10×10^{-5}
HI ^f (SUM)					6.00×10^{-3}	1.00×10^{-2}

^a Relative potency factors.^b Target hazard quotient.^c Acceptable daily intake (mg/kg Body Mass/day).^d Maximum concentration limits (mg/kg Body Mass/day).^e Hazard index.^f Index compound.**Table 9**

Estimated exposure percentiles for carcinogenic and non- carcinogenic metals.

Metal	EU ^a		ILCR ^b		HQ ^c	
	ADI ^d	CSF ^e	50 %	95 %	50 %	95 %
As	0.0001	1.5	2.25×10^{-7}	7.10×10^{-7}	1.50×10^{-3}	4.20×10^{-3}
Cd	0.001	–	–	–	1.50×10^{-4}	3.36×10^{-4}
Cr	0.005	–	–	–	3.00×10^{-5}	6.25×10^{-5}
Cu	0.5	–	–	–	7.84×10^{-5}	1.03×10^{-4}
Fe	0.8	–	–	–	4.00×10^{-4}	6.90×10^{-4}
Hg	0.0005	–	–	–	3.00×10^{-4}	6.10×10^{-4}
Ni	0.005	–	–	–	2.10×10^{-4}	4.83×10^{-4}
Pb	0.003	0.0083	1.24×10^{-9}	5.38×10^{-9}	5.00×10^{-5}	6.00×10^{-4}
Hazard Index (HI)	–	–	–	–	3.80×10^{-3}	7.08×10^{-3}
ILCR (SUM)	–	–	2.26×10^{-7}	7.15×10^{-7}	–	–

^a European union.^b Incremental Life Time Cancer Risk.^c Target hazard quotient.^d Acceptable daily intake (mg/kg Body Mass/day).^e Cancer slope factor (mg/kg Body Mass/day).

exceeded the values established by law (Quijano et al., 2016). In our study, HRA for oral exposure to 22 pesticides via consumption of date palm fruits showed unlikeliness of health risk to Iranian consumers. Similar results were reported from Brazil where 46 pesticides in peach, guava, kaki, and cashew apple, were determined. Over 70 % of the samples were positive for pesticides residue, with dithiocarbamates being present in 46.5 %, λ -cyhalothrin in 37.1 %, and omethoate in 21.8 % of the positive samples. HRA showed that intake of OPs or PYs via consumption of these fruits is unlikely to pose health risk to consumers (Jardim et al., 2014).

Our carcinogenic and non-carcinogenic scenarios for detected metals showed no significant health risk to Iranian consumers of date, and concentrations of metals were below their respective ADIs. It was reported that long biological half-lives, bioaccumulation potential, ubiquitous nature, toxicity, and non-biodegradability of metals allow them to accumulate in soil and plants and consequently, enter human body (Cabral-Pinto et al., 2019). A study from China assessed metals levels in 268 vegetables and associated soil samples and found that concentrations of metals were greater than MRLs (Liu et al., 2013). Also, measurement of metals in 343 vegetable samples revealed little risks posed

Table 10
Estimated exposure percentiles for polycyclic aromatic hydrocarbons (PAHs).

PAHs	TEF ^a	ILCR ^b		MoE ^c	
		50 %	95 %	50 %	95 %
Ace ^d	0.001	2.73×10^{-16}	5.33×10^{-16}	1.30×10^{10}	3.57×10^{10}
Acy ^e	0.001	2.73×10^{-16}	5.33×10^{-16}	1.30×10^{10}	3.57×10^{10}
Ant ^f	0.01	3.28×10^{-15}	6.18×10^{-15}	1.00×10^9	2.66×10^9
BaA ^g	0.1	8.72×10^{-14}	1.01×10^{-13}	4.00×10^7	6.19×10^7
BaP ^h	1.00	5.18×10^{-12}	8.44×10^{-12}	6.89×10^5	9.93×10^5
BbF ⁱ	0.1	2.19×10^{-14}	5.32×10^{-14}	1.63×10^8	4.15×10^8
BghiP ^j	0.01	2.73×10^{-15}	5.33×10^{-15}	1.30×10^9	3.48×10^9
BkF ^k	0.1	2.73×10^{-14}	5.34×10^{-14}	1.30×10^9	3.48×10^9
Chr ^l	0.01	5.47×10^{-15}	9.00×10^{-15}	6.53×10^8	9.15×10^8
DahA ^m	0.001	2.73×10^{-16}	5.33×10^{-16}	1.30×10^{10}	3.50×10^{10}
Fl ⁿ	0.001	1.64×10^{-16}	2.00×10^{-16}	2.17×10^{10}	5.63×10^{10}
Flu ^o	0.001	1.64×10^{-16}	2.00×10^{-16}	2.17×10^{10}	5.63×10^{10}
IcdP ^p	0.1	5.29×10^{-14}	8.85×10^{-14}	6.75×10^7	9.34×10^7
Nap ^q	0.001	1.64×10^{-16}	2.00×10^{-16}	2.17×10^{10}	5.63×10^{10}
Phe ^r	0.001	4.92×10^{-16}	7.60×10^{-16}	7.20×10^9	1.00×10^{10}
Pyr ^s	0.001	2.47×10^{-15}	5.00×10^{-15}	1.44×10^9	3.71×10^{10}
ILCR (SUM)		5.39×10^{-12}	8.76×10^{-12}	–	–
MoE (SUM)		–	–	1.16×10^{11}	2.97×10^{11}

^a Toxic equivalency factor.

^b Incremental life Time Cancer Risk.

^c Margins of Exposure.

^d Acenaphthene.

^e Acenaphthylene.

^f Anthracene.

^g Benzo[*a*]Anthracene.

^h Benzo[*a*]Pyrene.

ⁱ Benzo[*b*]Fluoranthene, ^jBenzo[*g,h,i*] Perylene, ^kBenzo[*k*]Fluoranthene, ^lChrysene.

^m Dibenzo[*a,h*]anthracene.

ⁿ Fluorene.

^o Fluoranthene.

^p Indeno[1,2,3-*cd*]pyrene.

^q Naphthalene.

^r Phenanthrene.

^s Pyrene.

by As, Cd, Pb or Hg to people in Zhejiang, southeast China (Huang et al., 2014).

In the present report on the assessment of exposure of humans to PAHs through consumption of date palm fruit, 900 samples of various cultivars collected from various regions was done. Based on calculated ILCR and MoE, PAHs residue levels posed *de minimis* risks to Iranian consumer's health. Reports from India showed PAHs contamination in several products. Risks of additional cancers due to chronic exposure to PAHs through consumption of several products in India showed that cancer risk ranged from *de minimis* to significant. Several pre-harvest factors, including atmospheric pollution and contamination of soils by application of sewage sludge and forest fires, as well as post-harvest manufacturing and cooking processes, can contaminate foods with PAHs, which can in turn cause adverse effects (Singh and Agarwal, 2018). In a previous study that analyzed various vegetables for eight PAHs, risk of additional cancers in males and females were 1.2×10^{-5} and 1.1×10^{-5} , respectively (Ding et al., 2013). Besides, a study from Taiyuan, China, showed that the risk of exposure to PAHs through diet was 9.07×10^{-4} - 1.12×10^{-4} in adults (Nie et al., 2014).

A report from Azerbaijan determined risks due to PAHs exposure through intake of different groups of foods (e.g. bread and bakery, potatoes, garden crops, meat, fishery and dairy products, fruit and berries, eggs, sugar and confectionery, vegetable oils and margarine). The potential carcinogenic risk for PAH exposure in the above-noted foods was 9.34×10^{-5} - 3.67×10^{-4} (Nwaneshiudu et al., 2007).

Additionally, dietary intake of PAHs was estimated for the general population of Catalonia, Spain. Results indicated that the estimated total daily intake of BaP would be associated with 4.50×10^{-6} increased risk of cancer development in male adults with a body weight of 70 kg (Martorell et al., 2010).

Alomirah et al. investigated the concentrations of 16 PAHs in various grilled and smoked foods and estimated the dietary exposure for Kuwaiti children, adolescents and adults. The estimated ILCR in Kuwaiti average adult associated with the dietary intake of PAHs through consumption of only grilled and smoked food items, was lower than the acceptable risk level (Alomirah et al., 2011).

In the current study, sensitivity analysis was performed to establish the most significantly influential factor among the input values employed for HRA. Concentrations of pesticides, metals and PAHs had the greatest effect on carcinogenic and non-carcinogenic risks. In another study, Body mass and per capita consumption had the greatest effect in a study that assessed hazardous risks of human exposure to metals (As, Pb, and Cd) through the consumption of rice (Sharafi et al., 2019). However, rates of ingestion represented the greatest effect risks posed by PAHs (Chiang et al., 2009).

5. Conclusions

In this work, cumulative risk of exposure of the general Iranian population to 22 pesticides, 6 metals, and 16 PAHs through consumption of date fruits, was assessed. Out of 900 date samples collected during 2018–2019, none exceeded MRLs set by the EU for any of the chemicals. Cumulative risk reflected as total HI value of three groups of pesticides, was <1.0. Metals, based on the calculated ILCRs, were not found to pose risk to Iranian consumers health; also, HI values for metals were <1.0. For PAHs, ILCR and MoE values did not indicate risks to health. Based on sensitivity analysis, concentrations of pesticides, metals and PAHs were all directly proportional to the estimated risks. In other words, we found that increased contaminant levels can directly enhance the risk. It generally seems that chronic cumulative pesticide, metals,

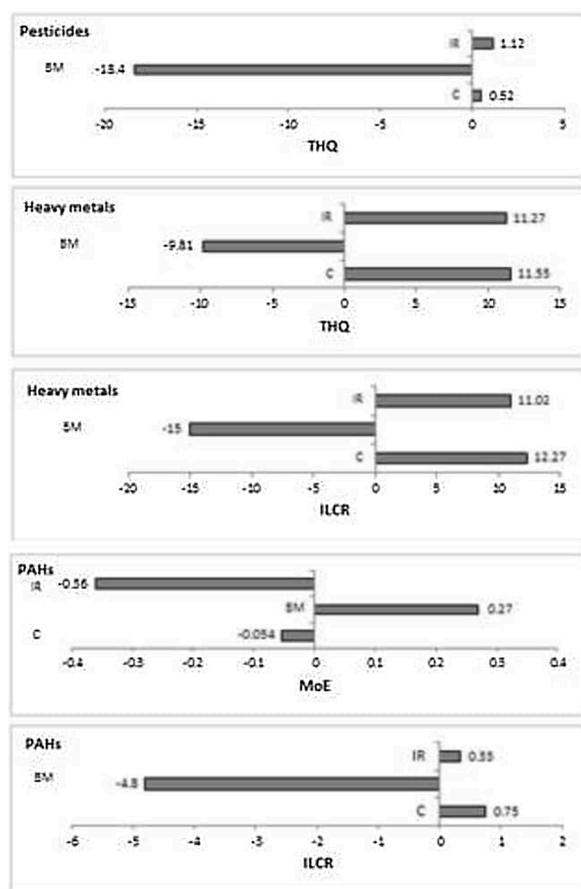


Fig. 2. Influential parameters (%) in HQ and ILCR for pesticides, metals, and polycyclic aromatic hydrocarbons (PAHs). HQ: Hazard Quotients; ILCR: Incremental Life Time Cancer Risk; MoE: Margins of Exposure; PAHs: Polycyclic Aromatic Hydrocarbons; IR: Ingestion Rate; BM: Body Mass; C: Concentration.

and PAHs intake through date consumption pose no health risk to Iranian consumers. Agricultural policies can be applied to manage risks by using cultivars with lower contaminant-accumulation probability, avoidance of farming near roads, and urban, industrial, and waste mining zones, and soil remediation, to make a more appropriate balance between environmental protection, food safety improvement, and health risks. Further studies are needed to assess pesticides, metals, PAHs intakes from consumption of other fruits and vegetables and their consequent risk to human health.

CRediT authorship contribution statement

Seyedeh Faezeh Taghizadeh: Formal analysis, Methodology, Software, Writing - original draft. **Ramin Rezaee:** Supervision, Validation, Writing - review & editing. **Majid Azizi:** Conceptualization, Investigation. **A. Wallace Hayes:** Investigation, Writing - review & editing. **John P. Giesy:** Funding acquisition. **Gholamreza Karimi:** Funding acquisition.

Declaration of Competing Interest

Authors declare that there is no conflict of interest.

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