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Polycyclic aromatic hydrocarbons in infant formulae, follow-on formulae, and baby foods in Iran: An assessment of risk

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ABSTRACT

Twenty-seven samples of infant formulae and follow-on formulae and fifteen samples of baby food from Iranian markets were analyzed for concentrations of four polycyclic aromatic hydrocarbons (PAH4) determined by use of gas chromatography coupled to mass spectrophotometry. An assessment of risks posed to infants and toddlers was conducted by calculating the margin of exposure and incremental lifetime cancer risk (ILCR) by use of the Monte Carlo Simulation Method. Benzo (a) anthracene, was not detected in any of the samples, while approximately 64.3% samples contained detectable amounts of benzo (a) pyrene, while chrysene was observed in three samples and benzo (b) fluoranthene was detected in one sample. One of the samples contained 1.43 μg PAH4/kg, which was greater than the maximum tolerable limit (MTL; 1 μg/kg) stated in Commission Regulation (EU) 2015/1125. Accordingly, the 95% ILCRs in the infants/toddlers due to ingestion of milk powder and baby foods were determined to be 1.3×10^{-6} and 7.3×10^{-7}, respectively. Also, the 95th centiles of the MOEs, due to ingesting milk powder or baby foods by infants/toddlers were estimated to be 3.6×10^{4} and 7.2×10^{4}, respectively. In Iran, infants and toddlers are not at serious health risk (MOE $\geq 1 \times 10^{4}$ and ILCR $< 1 \times 10^{-4}$).

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are comprised of two or more fused aromatic rings (Wang et al., 2018). It has been shown that PAHs are produced by pyrolysis of organic substances and incomplete combustion (Belo et al., 2017; Wang et al., 2018). Except for smokers, injection of food is the predominant route of exposure of humans to these carcinogens (Iwegbue et al., 2014; Rozentale et al., 2017). PAHs occur in foods, not only due to environmental conditions (i.e. deposition on vegetable leaves), but can be created by heat treatment such as grilling, smoking, and smoke-drying (de Lima et al., 2017; Rozentale et al., 2017).

Based on toxic potency, benzo (a) anthracene (BaA), chrysene (Chr), benzo (b)fluoranthene (BbF) and benzo (a) pyrene (BaP) are the most important PAHs, and their sum has been defined as PAH4 (Rozentale et al., 2017). Chronic exposure to PAHs can result in skin inflammation, cataracts, asthma-like symptoms and kidney damage. Also, teratogenic, genotoxic, and immunotoxic effects of these compounds have been

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documented (Rengarajan et al., 2015). The International Agency for Research on Cancer (IARC) has categorized BaP as a known carcinogen to humans (group 1A). In addition, BaA, Chr, and BbF are listed as possibly carcinogenic to humans (group 2B) (Iwegbue et al., 2014).

Safe and sufficient diets are essential for growth of babys. Because of their vulnerability, infants and toddlers are sensitive to noxious effect of toxicants. In comparison with adults, infants exhibit greater absorption capacity, lesser ability to detoxify and lesser ability to metabolize residues. Once carcinogenic compounds, such as PAHs are absorbed, they are able to distribute into various tissues, particularly those of greater lipid content (Rey-Salgueiro et al., 2009). As children grow their bodies need greater quantities of food. Therefore, they are at greater risk of dietary exposure to food contaminant. Hence, postnatal exposure to food contaminant is of concern (Santonicola et al., 2017b).

Products consumed by infants and toddlers, such as formula milk, canned fruits and vegetables, and baby food are used as alternatives to breast milk (Nepalia et al., 2017). In accordance with conclusions by the medical community, when breast feeding is not sufficient or possible, infant formulas are the best choice for feeding. Baby food is defined as any food which can be used by infants and toddlers during the period of ages of 6 months to 2 years (Nepalia et al., 2017). European regulations have set 1 μg/kg as permissible concentration for the sum of the four PAHs constituting PAH4 in infant formulae, follow-on formulae, processed cereal-based foods and baby foods (Purcaro et al., 2013).

Manufacturing conditions and environmental contamination are two important factors affecting PAHs content of milk powders (Amirdivani et al., 2019; Ciecierska and Obiedziński, 2010).

Food standards agency (FSA) evaluated PAHs levels in 97 samples of infant formulae milk, collected from across the UK. In 39 samples, BaP level was found to be lower than 1.0 μg/kg (FSA (Food Standards Agency), 2006). Kishikawa and co-workers determined PAHs concentration in baby food samples. They found that PAHs levels were about 2.0 ± 0.30 μg/kg (Kishikawa et al., 2003; Yebra-Pimentel et al., 2015). In a research, PAH levels of different type of milk and its products including infant milk, skimmed milk, yogurt and soy milk were determined. Although no PAHs were determined in infant milk, low concentrations of fluorene (0.83–1.04 μg/L) and pyrene (0.63–1.12 μg/L) were detected in full fat milk (Bansal and Kim, 2015). In another study, 7 PAH compounds were determined in samples of milk powder. PAHs concentration were in the range of 0.244–0.775 μg/kg.

In France, a total diet study (TDS) was performed during the 2010 and 2016 to evaluate the risk associated with to heat-induced compounds such as PAH_S, acrylamide and furan in food of non-breast-fed children from 1 to 36 months old. Dietary exposure was measured for infants using food consumptions documented through a 3-consecutive-days record. Findings of this study showed that margins of exposure (MOE) values for PAHs was higher than 10 000, representing safety of food samples for infants and toddlers (Sirot et al., 2019). It was exhibited that maternal exposure to PAH in electronic-waste contaminated areas associated with adverse birth outcomes. Presence of hydroxylated PAH metabolites was confirmed in maternal urine samples of pregnant women. A close correlation was observed with PAH metabolite concentration and decrease 234 g in weight, 1.7 cm in head circumference and 1.1 kg m^2 in body mass index BMI (Huo et al., 2019). A recent study stated that the level of PAH in breast milk of obese women is significantly higher, when compared with that of normal mothers. BaP, BkF, BaA and BbF were of the predominant PAHs (Acharya et al., 2019). In urban asthmatic children, BaP attributed with concurrent suppression of inflammatory indices such as NF-kB. BaP not only increase heme biosynthesis, but also decrease $CD71^+$ erythroids and Natural killer T (NKT) lymphocytes (Choi et al., 2019).

Due to relatively great fat content, infant formula is valuable nutrition providing not only energy, but also produce suitable matrix for fat soluble vitamins. Since triglycerides have similar polarity to those of the PAH4, presence of fat facilitates contamination during preparation of samples for quantification of PAH4 (Nyiri et al., 2017). Among the various preparation techniques, solid phase extraction (SPE) is method of choice to meet sensitivity and rapidity requirements. In several applications, SPE is used as a single combined extraction and clean-up step (Bogusz et al., 2004; Moret and Conte, 2002). In 2009, by using Sep-Pack silica plus cartridges® as SPE mini columns, PAHs were quantified in infant foods (Rey-Salgueiro et al., 2009). In silica-based cartridges, triglycerides are retained, while PAHs can be eluted by n-hexane as the solvent mobile phase (Purcaro et al., 2013). Currently several instruments, including high performance liquid chromatography (HPLC), liquid chromatography tandem mass spectroscopy (LC-MS/MS), and gas chromatography mass spectroscopy (GC-MS) have been employed for identification and quantification of PAHs (Nyiri et al., 2017; Rey-Salgueiro et al., 2009; Wang et al., 2018).

Since health is associated with various variables and factors, evaluation of risk is a complicated process. Estimation of risk by single-point values can result in uncertainties (Fathabad et al., 2018). Monte Carlo Simulation (MCS) can be applied to evaluate uncertainties during assessment of risks associated exposure of humans to contaminants. MCS is proposed for quantification of uncertainty and variability (Keramati et al., 2018; Razzaghi et al., 2018; Yousefi et al., 2018). Moreover, Sensitivity analysis is performed to identify the most important variable which affect accuracy of risk assessment (Xia et al., 2013).

In the study, results of which are presented here, concentrations of PAH4 were quantified in common brands of infant formula, follow-on formula, and baby-food in Iran. In addition, risks to health due to injection of food by infants and toddlers were determined by calculating the margin of exposure (MOE), while incremental lifetime cancer risk (ILCR) was estimated by use of the MCS method.

2. Material and methods

2.1. Reagents and materials

All chemicals and reagents were of analytical grade. benzo (a) anthracene (BaA), chrysene (Chr), benzo (b) fluoranthene (BbF), benzo (a) pyrene (BaP) and triphenyl phosphate (TPP) were procured from Sigma-Aldrich (Steinheim, Germany). n-hexane and acetone were purchased from Merck Chemical Company (Darmstadt, Germany). Anhydrous sodium sulfate (purity 99%) obtained from BDH (Poole, UK). Sep-Pak silica plus long cartridges (690 mg sorbent per cartridge, 55–105 μm particle size) supplied by Waters (Wexford, Ireland).

Stock solutions of PAHs at 1000 mg L^{-1} were prepared in n-hexane wrapped in aluminum foil. In addition, TPP stock solution was provided in acetone at 1000 mg L^{-1}. To prevent volatilization and photodegradation, stock solutions were stored in the dark at 4 °C. Also, more diluted solutions at 10 mg L^{-1} were prepared monthly. A working standard mixed solution was prepared daily by diluting with n-hexane.

2.2. Instruments

Identification and quantification were accomplished by use of GC analyses with a Agilent 6890 N (Agilent, Waldbronn, Germany) gas chromatograph, coupled to a Agilent 5975 quadrupole mass selective spectrometer equipped with an inert ion source and provided with a split–splitless injection port. The carrier gas helium was maintained at a constant pressure of 13.00 psi and purge flow of 30.0 ml/min. A DB-5MS (Agilent) capillary column (5% diphenyl- 95% dimethyl polysiloxane) (30 m × 0.25 mm i.d., 0.25 μm film thickness) was used. Operating conditions were as follows: helium carrier gas 1.5 ml/min (constant flow); injector temperature 300 °C, pulsed splitless, injection volume of 1 μL; the ion source, transfer line, and quadrupole temperature 300 °C, 280 °C, and 180 °C, respectively; the GC oven temperature program: 55 °C (1 min), 55–290 °C (25 °C/min), (3 min). The quadrupole analyzer measured the abundance of ions of m/z from 45 to

450 and detector voltage was 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 M., 2005). PAHs were identified based on comparisons of observed GC retention time with those of standard solutions of PAHs and use of characteristic ions.

2.3. Sample collection and preparation

Twenty-seven samples of baby milk powder and fifteen samples of baby food were collected from retail markets of Iran. Samples of baby milk included: infant milk formulae (0–6 months) coded as A1, B1, and C1 (n = 3); Follow-on formulae (6–12 months) coded as A2, B2, and C2 (n = 3); Follow-on formulae (1–2 years) coded as A3, B3, and C3 (n = 3). Samples of baby food included wheat + milk, honey + wheat with milk, wheat + palm with milk, banana + wheat with milk and fruit + wheat with milk (n = 3). Within a given brand, 3 samples with different dates of manufacture were purchased and composited. From this, a subsample was taken for analysis. All samples were refrigerated prior to analyses (Iwegbue et al., 2014).

The pre-analytical treatment was relied on a method for the determination of PAHs in infant foods, smoked foods, and instant coffee previously reported by other researchers (Falcón et al., 1996; Garcí;a-Falcón et al., 2005; Rey-Salgueiro et al., 2008; Rey-Salgueiro et al., 2009). 1.0 g of samples spiked with TPP as an internal standard (IS) (Szelewski M., 2005) were subjected to ultrasound-assisted solvent extraction with 3 × 10 mL n-hexane/acetone (95:5 v/v) for 10 min each in an amber glass vials (Oh et al., 2016; Ciecierska and Obiedziński, 2010). Solvent extracts were filtered (filter paper) and passed through a column packed with anhydrous Na_2SO_4 (Ciecierska and Obiedziński, 2010). In next step, solutions were cleaned-up, using Sep-Pack silica plus cartridges® (Wexford, Ireland) that had been preconditioned with 10 mL n-hexane. Then, 10 mL hexane/acetone (95:5 v/v) added to avoid loss. With the help of a gentle stream of nitrogen, the elute was evaporated until about 1 mL. The obtained elute filtered with PTFE filter (0.45 μm) and transferred to amber vial glass and evaporated till full dryness. Finally, re-dissolved in 0.2 mL n-hexane for GC-MS analysis.

2.4. Quantification and method validation

Quality assurance and Quality control were ensured by quantification of recoveries from matrix spikes. Compounds quantification was performed by using an internal standard method. Calibrations were obtained with PAH solutions at six concentrations.

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 (Moudgil et al., 2019; Wang et al., 2018). Coefficients of determination (R^2) values obtained were between 0.991 and 0.997. The limit of detection (LOD), defined as signal to-noise 3:1, and the limit of quantification (LOQ), defined as signal to-noise 10:1 (Lee et al., 2018), as well as recovery experiments were carried out. Accuracies were determined by spiking samples of infant milk formula and infant food with three different concentrations of PAH4 standards (Ciecierska and Obiedziński, 2010). Method precision was analyzed by intraday and inter-day assays at three concentrations each day for three consecutive days (Table 1).

2.5. 5. Characterization cancer risk

Assessment of ILCR, recommended by United States Environmental Protection Agency and MOE suggested by World Health Organization and EFSA Scientific Committee (EFSA, 2005) were employed (Tables 2 and 3) (Lee et al., 2018). Daily dietary intakes of PAHs (E_D) were calculated based on published methods (Li et al., 2016b; Xia et al., 2010) (Equations (1-3).SS

$$E_D = \sum_{i=1}^{n} BEC \times IRi \quad (1)$$

$$BEC = \sum_{i=1}^{n} C \times TEFi \quad (2)$$

Concentrations of PAH4 were converted to concentrations of benzo (a) pyrene equivalents (BaP_{eq}; μg kg^{-1}), (BEC) in infant formulae, follow-on formulae, and baby foods by use of toxicity equivalency factors (TEFs). Values of TEF_i for BaA, Chr, BbF and BaP are 0.1, 0.001, 0.1 and 1, respectively (Xia et al., 2010). IR and C are ingestion rate of food and concentration of PAH congener in food, respectively (Xia et al., 2010).

2.5.1. Calculation of ILCR

Cancer risk correlated with consumption of infant formulae, follow-on formulae and baby foods were calculated, based on previously published methods (Li et al., 2016a; Tian et al., 2018) (Equation (3)).

$$ILCR = E_D \times EF \times ED \times CSF \times CF/(BW \times AT) \quad (3)$$

Where ILCR is incremental lifetime cancer risk (dimensionless); E_D is the daily dietary PAH exposure level (ng day^{-1}), EF is exposure frequency (365 day $year^{-1}$), ED is duration of exposure (years), CSF is the oral cancer slope factor of BaP with geometric mean of 7.3 [(mg/kg)/day] (Srivastava et al., 2017), CF is conversion factor (10^{-6} g ng^{-1}), BW is the body weight and AT is mean time for development of carcinogens (25 550 days) (Fakhri et al., 2018; Li et al., 2016b; Shahrbabki et al., 2018; Taghizadeh et al., 2017, 2018).

2.5.2. Calculation of MOE

The MOE, which is the inverse of the risk, is another approach to evaluate the risk compounds such as PAH4, which exhibited both carcinogenic and genotoxic effects (Santonicola et al., 2017b). By dividing the Benchmark Dose Lower Limit ($BMDL_{10}$) with the estimated daily intake (EDI), MOE can be calculated (Suparmi et al., 2018). $BMDL_{10}$ is the lower bound of a 95% confidence interval on the benchmark dose corresponding to a 10% tumor incidence in test animal (Iwegbue et al., 2014). EDI was calculated by use of previously published methods (Rahmani et al., 2018; Santonicola et al., 2017b) (Equation (4)).

$$EDI = \frac{Ci \times IRi}{BW} \quad (4)$$

2.6. Uncertainty analysis for carcinogenic risk

MCS (n = 10000) was used to evaluate the uncertainties and its impact on the risk estimation. This probabilistic modeling, employing the entire range of input variable to develop a probability distribution of exposure or risk rather than a single point data (Zhou et al., 2011). The model input parameters applied in the simulation was showed in Table 3. The MCS and sensitivity analysis were all implemented by Oracle Crystal Ball (version 11.1.4512.0). All values were extracted from Oracle Crystal Ball and then figures plotted by employing Origin 2018 software (version: 9.50.00).

2.7. Sensitivity analysis

Sensitivity analysis was conducted to identify the most significant input data and risk model factors that affected the output values (Zhou et al., 2011). Input variables were $BaP_{eq.}$, ED, EF, IR, CSF, CF, BW, AT and $BMDL_{10}$.

Table 1
Method linear range (μg/kg), coefficient of determination (R^2), % recovery (mean ± SD) and intra-day/inter-day value (RSD,%) of PAH4 (n = 3).

PAH4	Linear range	R^2	Recovery in infant formula Spike level (μg/kg)			Recovery in baby food Spike level (μg/kg)			Intraday variation Spike level (μg/kg)			Interday variation Spike level (μg/kg)		
			0.25	1.5	6	0.5	2	6	1.5	3	5	1.5	3	5
BaA	0.1–6	0.997	75.2 ± 6.1	74.3 ± 6.1	81 ± 10.4	92.2 ± 8.2	80.0 ± 9.1	80.3 ± 4.3	13.5	5.1	7.4	10.7	7.9	2.7
Chr	0.1–6	0.994	75.2 ± 7.1	73.5 ± 6.3	86.3 ± 5.5	78.2 ± 5.3	77.1 ± 5.3	83.5 ± 6.1	9.9	10.8	10.3	11.6	12.9	9.1
BbF	0.1–6	0.991	84.5 ± 8.2	75.3 ± 5.7	82.5 ± 7.7	84.1 ± 16	79.6 ± 7.6	80.3 ± 3.7	9.0	8.4	10.1	11.6	10.0	2.2
BaP	0.1–6	0.993	78.5 ± 2.1	79.3 ± 1.3	77.6 ± 1.5	60.0 ± 9.5	74.8 ± 9.6	71.3 ± 4.2	13.0	11.4	6.9	4.8	11.4	4.5

3. Results

3.1. Method validation

European Commission Regulation (EC) No. 333/2007 defines the conditions for approaches for analysis for BaP as follows: LOD < 0.3 μg/kg, LOQ < 0.9 μg/kg, recovery from 50 to 120%. LOD of BaA, Chr, BbF and BaP calculated 0.02, 0.05, 0.04 and 0.04 μg/kg, respectively. LOQ values for these compounds were 0.11, 0.17, 0.14 and 0.16 μg/kg, respectively. Recoveries for PAH4 were in the acceptable range, which demonstrated accuracy of the analyses (Soceanu et al., 2016) (Table 1).

3.2. PAH4 profile in infant formulae and follow-on formulae

Results, which are presented here, revealed that none of the infant formulae or follow-on formulae were contaminated with BaA (Table 4). Chr was detected in 22.2% of samples with concentrations from 0.53 ± 0.06 to 0.95 ± 0.11 μg/kg. BbF was determined in 11.1% of infant formulae and follow-on formulae. Concentrations of BaP in 55.5% of samples exceeded the limit of quantification.

3.3. PAH4 profile of baby foods

Similar to infant formulae and follow-on formulae, in baby foods, concentrations of BaA were less than the limit of quantification. Concentrations of Chr were detected in 20% of baby foods with a mean of 0.18 ± 0.01 μg/kg. BaP detected in 80% of baby food samples, at concentrations ranging from 0.190 ± 0.02 to 0.48 ± 0 .04 μg/kg. Concentrations of BbF did not exceed the limit of quantification in any sample of baby foods.

3.4. Risk assessment of PAH4 based on ILCR

Results demonstrated that ILCR values for infant formulae and follow-on formulae ranged from 1.7×10^{-7} to 1.2×10^{-6} (obtained from single point values) (Table 5). C3 and A2 exhibited the greatest values for ILCR, which were 1.3×10^{-6} and 1.1×10^{-6}, respectively. In baby foods, ILCR values ranged from 3.1×10^{-7} to 7.1×10^{-7}. Based on MCS, 95th centiles for the ILCR in infants/toddlers resulting from ingestion of milk powders and baby foods were estimated to be 5.6×10^{-6} and 3.1×10^{-7}, respectively (Figs. 1 and 2). 50th centiles (mean) ILCR values for infants and toddlers were 1.1×10^{-6} and 1.4×10^{-7}, respectively (Figs. 1 and 2).

3.5. Risk assessment of PAH4 based on MOE

MOE, which are the inverse of risk quotients (RQ) was calculated for infants and toddlers (Table 5). Rely on single point values, least values for MOE values were observed for A2, for which MOEs were 3.3×10^3, 7.0×10^3, and 1.2×10^4, for BaP, PAH2 (sum of BaP and Chr)) and PAH4, respectively. Maximum values observed for MOE in A3 and B3 were 2.7×10^4, 3.1×10^4 and 3.6×10^4 for BaP, PAH2, and PAH4, respectively. In baby food samples, the greatest MOEs were observed in samples of wheat + milk were 4.8×10^4, 5.7×10^4, and 6.4×10^4, for BaP, PAH2, and PAH4, respectively Also, The least MOEs for BaP, PAH2, and PAH4, which were 1.6×10^4, 2.9×10^4, and 4.2×10^4, respectively were observed in samples of wheat + palm. Employing MCS, 95th centiles MOE for consumption of milk powders and baby foods for infants/toddlers were estimated to be 2.1×10^5 and 6.1×10^5, respectively (Figs. 3 and 4). The 50th centiles MOE for intake of milk powders and baby foods for infants and toddlers were predicted to be 3.4×10^4 and 3.5×10^5, respectively (Figs. 3 and 4).

3.6. Parameters sensitivity analysis

The quantitative sensitivity analysis was conducted to determine the greatest effects of input parameters on the health risk assessment of milk powder and baby food (Yang et al., 2015). The most significantly influential parameters which determined by sensitivity analysis during the MCS were shown (Fig. 5–8). Results revealed that Σ $BaP_{eq.}$ (0.69), ED (0.42) and IR (0.30) were the most sensitive variables on risk assessment of milk powder samples. For baby foods, Σ $BaP_{eq.}$ (0.65), ED (0.22) and CSF (0.34) were the most influential parameters. In both samples of milk powder and baby food, BW contributed −0.19 and −0.07, respectively. When risk analysis conducted by MOE, BW had the greatest effect on risk estimates.

Table 2
Factors applied for single-point calculation of ILCR and MOE.

Exposure parameters	Units	Infants (0-6a)	Infants (6-12a)	Toddlers (1–2 b) (milk powder)	Toddlers (6 a −2 b) (baby food)	References
Exposure frequency (EF)	days/year	365	365	365	365	Srivastava et al. (2017)
Exposure duration (ED)	Year	0.5	0.5	1	1.5	Bacigalupo and Hale (2012)
Ingestion rate (IR)	g/day	120	160	200	100[c]	Iwegbue et al. (2014)
Body weight (BW)	Kg	5.9	9.3	12.2	11	Iwegbue et al. (2014)
Averaging life span (AT)	Days	25550	25550	25550	25550	Srivastava et al. (2017)

[a] implies month.
[b] represents year.
[c] means based on manufactory order.

Table 3
Values and probability distributions of parameters in Monte Carlo analysis.

Definition	Units	Distribution	infant	toddler	References
Exposure frequency (EF)	days/year	–	365	365	Srivastava et al. (2017)
Exposure duration (ED)	Year	Uniforma	0–2	0.5–2	Wu et al. (2011)
Ingestion rate (IR)	g/day	LN[b]	130 ± 85	39 ± 3	(Clark et al., 2011; Morisset et al. (2013))
BaP cancer slope factor (CSF)	[(mg/kg)/day]	LN	7.3 ± 1.56	7.3 ± 1.56	Yang et al. (2015)
Conversion factor (CF)	g/ng	–	0.000001	0.000001	Watanabe et al. (2009)
Body weight (BW)	Kg	LN	7.5 ± 3.2	11.2 ± 0.55	Clark et al. (2011)
Averaging life span (AT)	Days	–	25550	25550	Yang et al. (2015)
Benchmark Dose Lower Limit ($BMDL_{10}$)	mg/kg bw/day	–	0.34	0.34	Santonicola et al. (2017a)

[a] For uniform distribution, the values were presented as minimum and maximum.
[b] For Log-normal (LN) distribution, the values were expressed as geometric mean and geometric standard deviation.

Table 4
Concentrations (Mean ± SD, μg/kg) of individual PAHs included in PAH4 in samples of infant formula, follow-on formula, and baby food (n = 3).

Sample	BaA	Chr	BbF	BaP
A1	< 0.11	0.95 ± 0.11	< 0.14	< 0.16
B1	< 0.11	< 0.17	< 0.14	0.57 ± 0.19
C1	< 0.11	< 0.17	< 0.14	0.59 ± 1.0
A2	< 0.11	< 0.17	0.19 ± 0.03	1.24 ± 0.28
B2	< 0.11	0.53 ± 0.06	< 0.14	< 0.16
C2	< 0.11	< 0.17	< 0.14	0.71 ± 0.09
A3	< 0.11	< 0.17	< 0.14	< 0.16
B3	< 0.11	< 0.17	< 0.14.	< 0.16
C3	< 0.11	< 0.17	< 0.14	0.73 ± 0.06
Wheat + hony	< 0.11	< 0.17	< 0.14	0.35 ± 0.09
Wheat + fruit	< 0.11	< 0.17	< 0.14	0.19 ± 0.03
Wheat + palm	< 0.11	< 0.17	< 0.14	0.48 ± 0.04
Wheat + milk	< 0.11	< 0.17	< 0.14	< 0.16
Wheat + banana	< 0.11	0.18 ± 0.01	< 0.14	0.19 ± 0.02

A1, B1 and C1 are infant formula (0–6 months).
A2, B2 and C2 are follow-on formula (6–12 months).
A3, B3 and C3 are follow-on formula (1–2 years).

4. Discussion

Concentrations of PAH4 listed by the EU Scientific Committee on Food were determined in the most consumed brands of infant formulae, follow-on formulae, and baby food in Iran.

According to the EU 2015/1125 dated 10 July 2015, the maximum tolerable limit for BaP and sum of PAH4 in the group of infant formulae, follow-on formulae, and baby foods has been set at a concentration of 1 μg/kg (Commission, 2015). In this study, except for one product, A2, which contained 1.43 ± 0.30 μg/kg (sum of PAH4), the other samples complied with EU criteria. The results of this study were consistent with results of previous studies. In 2017, concentrations of 14 PAHs most important PAH listed by Commission Regulation (EC) No. 1881/2006 were detected by high-pressure liquid chromatography with fluorescence detector in 30 samples of the Italian infant formulae. In this study, concentrations of BaP ranged from 0.00 to 1.66 μg/kg (with mean of 0.46 μg/kg) (Santonicola et al., 2017b). In a study, using GC-MS, performed in Nigeria, concentrations of PAHs in various infant formulae and follow-up formulae. Herein, different infant formulae including 0–6 months, 6–12 months, 1–3 years and 0–12 months were analyzed. Concentrations of BaP in all samples was less than 1 μg/kg, with a range of < 0.001–0.165 μg/kg). Also, the concentration of PAH4 in these products varied from < 0.001 to 0.651 μg/kg (Iwegbue et al., 2014). In a study conducted in Poland, infant formulae, follow-on formulae and baby foods were monitored for PAHs presence. In most samples, none of the 15 PAHs were observed, while BaP was only determined in two kinds of soups at lesser concentrations than the legal limit (Ciecierska and Obiedziński, 2010). In another study, occurrences of 11 PAHs and their hydroxylated metabolites were quantified in 17 infant cereals and 19 infant formulae. Only benzo (k) fluoranthene (BkF) was found at concentrations of 0.30 and 0.10 μg/kg in one sample of cereal and milk, respectively (Rey-Salgueiro et al., 2009). Recently, in a study of presence of PAHs in milk and meat/fish based baby food from Italy showed that concentrations of BaA, Chr, BbF and BaP in milk based baby foods were in the range 0.00–4.05, 0.00–6.68, 0.00–2.94 and 0.06–2.09 μg/kg, respectively. In addition, these contaminants in meat/fish based baby foods were in the range of 0.00–2.39, 0.00–2.11,

Table 5
Concentrations of Σ BaP equivalency (μg/kg), ILCR, EDI (ng/kg bw/day) and MOE for infant formula, follow-on formula and baby food.

Category	Sample	Σ BaP eq.	ILCR[a]	EDI			MOE[a]		
				BaP	PAH2	PAH4	BaP	PAH2	PAH4
Infant formula (0-6a)	A1	0.19	2.0×10^{-7}	3.25	22.60	27.68	2.1×10^{4}	7.5×10^{3}	1.2×10^{4}
	B1	0.57	6.1×10^{-7}	11.12	14.56	19.65	6.3×10^{3}	1.2×10^{4}	1.7×10^{4}
	C1	0.61	6.5×10^{-7}	11.95	15.41	20.50	5.8×10^{3}	1.1×10^{4}	1.7×10^{4}
Follow-on	A2	1.27	1.1×10^{-6}	21.36	24.29	29.40	3.3×10^{3}	7.0×10^{3}	1.2×10^{4}
Formula (6 -12a)	B2	0.18	1.7×10^{-7}	2.75	11.93	16.24	2.5×10^{4}	1.4×10^{4}	2.1×10^{4}
	C2	0.74	6.6×10^{-7}	12.30	15.22	19.53	5.7×10^{3}	1.1×10^{4}	1.7×10^{4}
Follow-on	A3	0.18	3.2×10^{-7}	2.62	5.41	9.51	2.7×10^{4}	3.1×10^{4}	3.6×10^{4}
Formula (1–2b)	B3	0.18	3.2×10^{-7}	2.62	5.41	9.51	2.7×10^{4}	3.1×10^{4}	3.6×10^{4}
	C3	0.75	1.3×10^{-6}	11.94	14.72	18.82	5.9×10^{3}	1.1×10^{4}	1.8×10^{4}
Baby food (6a – 2b)	Wheat + honey	0.37	5.3×10^{-7}	3.14	4.69	6.96	2.2×10^{4}	3.6×10^{4}	4.9×10^{4}
	Wheat + fruit	0.21	3.1×10^{-7}	1.73	3.27	5.54	4.0×10^{4}	5.2×10^{4}	6.1×10^{4}
	Wheat + palm	0.50	7.1×10^{-7}	4.333	5.89	8.16	1.6×10^{4}	2.9×10^{4}	4.2×10^{4}
	Wheat + milk	0.18	2.6×10^{-7}	1.45	3	5.27	4.8×10^{4}	5.7×10^{4}	6.4×10^{4}
	Wheat + banana	0.37	3.1×10^{-7}	1.74	3.29	5.56	4.0×10^{4}	5.2×10^{4}	6.1×10^{4}

[a] represents month.
[b] shows year.
[a] means obtained from single point values.

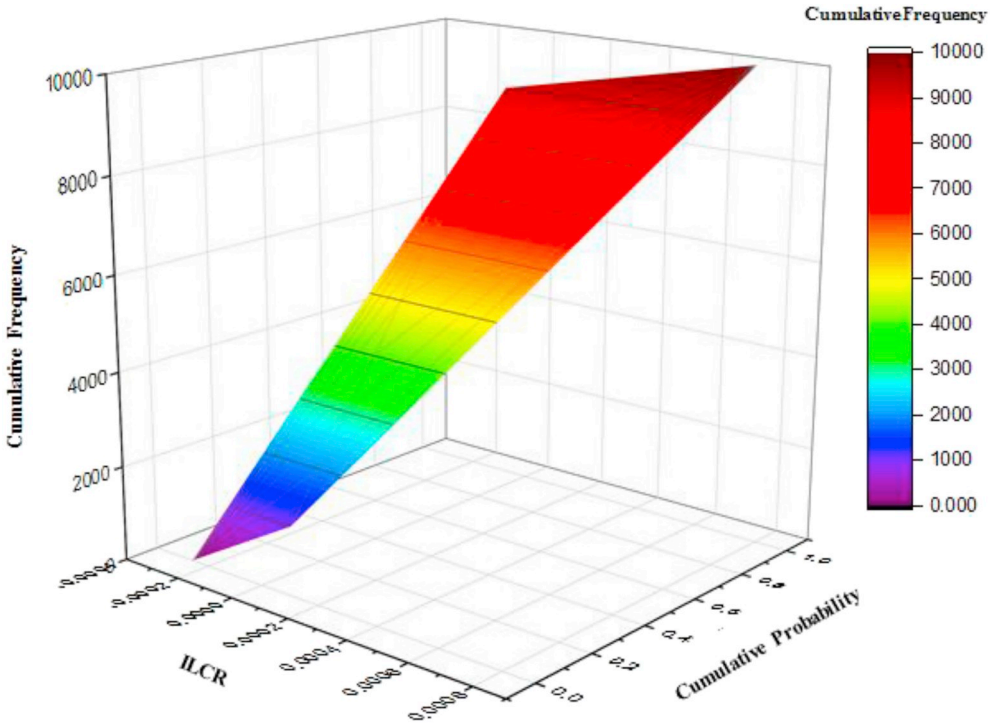

Fig. 1. Estimation of ILCR for infants due to consumption of PAH4 occurred in milk powder (E means × 10).

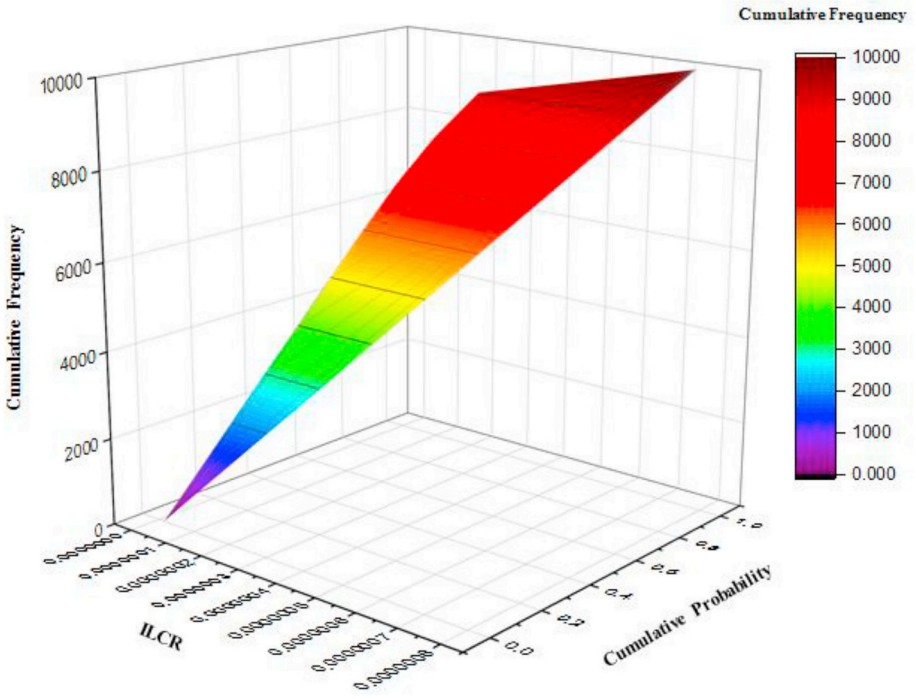

Fig. 2. Estimation of ILCR for infants due to consumption of PAH4 occurred in Baby food (E means × 10).

0.00–1.16 and 0.06–1.66 μg/kg, respectively (Santonicola et al., 2017a).

Except for smokers and occupational exposure, ingestion via food is one of the important routes of PAHs uptake along with dermal exposure. Concentrations of PAHs in dietary sources are a function not only of environmental state, but also thermal conditions. In the case of infant formulae and follow-on formulae, occurrence of PAHs is a function of conditions of drying as well as contamination of the source products (Iwegbue et al., 2014). PAHs can contaminate grass and feed ingredients of ruminants. When compared with rural areas, grass in industrial regions can contain these compounds at concentrations as much as eight-fold greater (García Londoño et al., 2017). Contamination of vegetables and fruits as the result of air deposition, irrigation with polluted water and soil uptake are other routes which affect concentration of PAH in final products (Cho and Shin, 2012). Alternatively, heat processes such as spray drying and evaporation can result

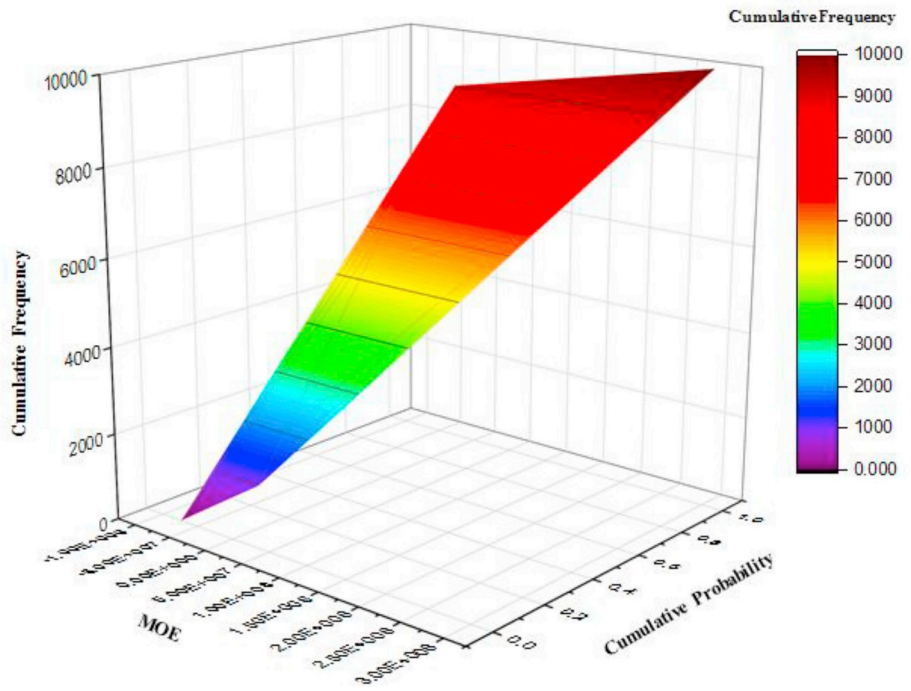

Fig. 3. Estimation of MOE toddlers due to consumption of PAH4 occurred in milk powder.

in formation of carcinogenic or genotoxic PAHs (Cho and Shin, 2012).

Determination of eight compounds (PAH8) including BaP, Chr, BkF, BaA, BbF, dibenz (a,h) anthracene (DahA), indeno (1,2,3-cd) pyrene (IcdP), benzo (ghi) perylene (BghiP) is appropriate for monitoring of PAHs in food. However, when compared with PAH4, PAH8 does not offer much added value (Zelinkova and Wenzl, 2015).

Due to vulnerability of infants and toddlers to carcinogenicity of PAH4, the assessment of potential health impacts of PAH4 in infant formula and infant foods seems crucial (Benford et al., 2010). USEPA defines that a level of risk where there is a lifetime cancer risk of one in a million (10^{-6}) over a 70-year lifetime period, is considered acceptable, while an instance where there is an additional lifetime cancer risk of one in ten thousand or greater (10^{-4}), is considered serious (Nie et al., 2014). In our study, the 95% ILCRs in the infants/toddlers due to ingestion of milk powder and baby foods were determined to be 5.6×10^{-6} and 3.1×10^{-7}, respectively. Hence, the consumption of milk powders and baby foods does not possess serious risk for infants and toddlers.

Use of the MOE is recommended by EFSA Scientific Committee to estimate risk level of carcinogenic and genotoxic PAH (EFSA, 2005). The MOE of 1×10^4 or higher signifies low public health concern (Yousefi et al., 2018). The 95th centiles of the MOEs, due to ingesting

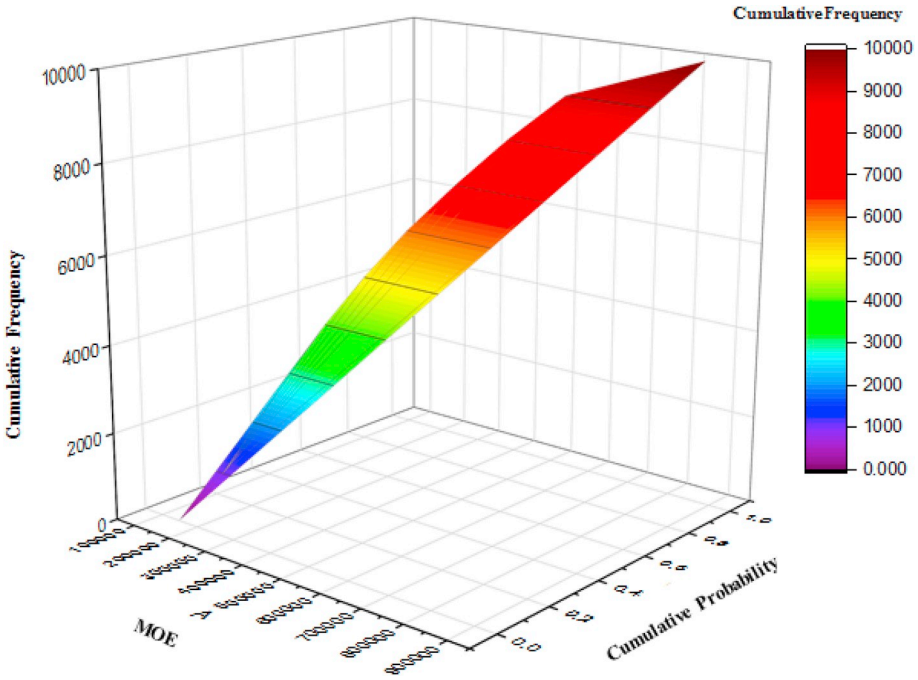

Fig. 4. Estimation of MOE for toddlers due to consumption of PAH4 occurred in Baby food.

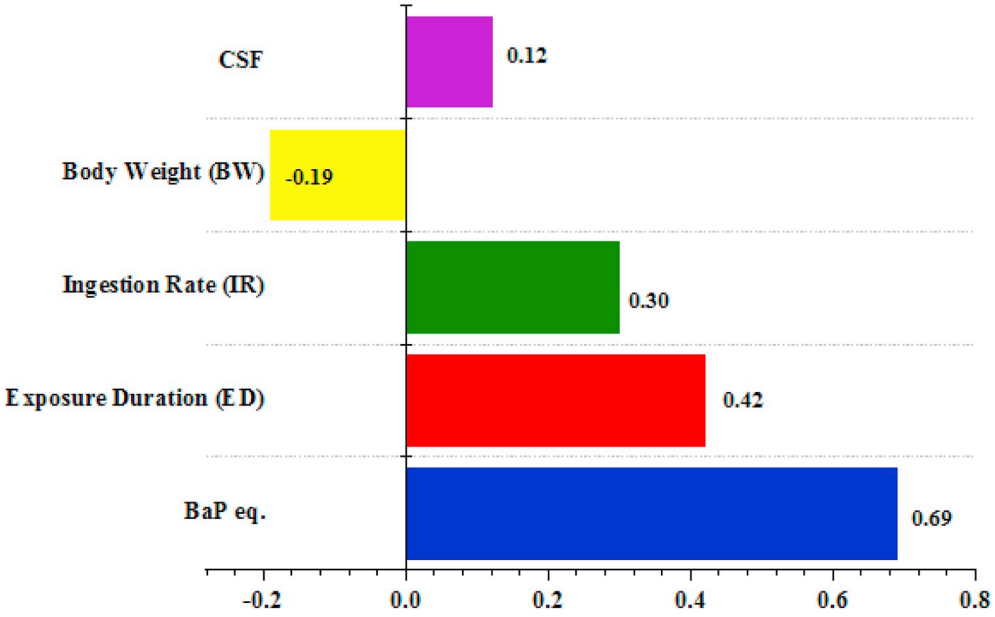

Fig. 5. Influential parameters in ILCR (Milk powder).

milk powder or baby foods by infants/toddlers were estimated to be 2.1×10^5 and 6.1×10^5, respectively. Hence, the consumption of milk powders and baby foods does not possess serious risk for infants and toddlers.

It should be mentioned that a significant difference was observed between MOE values obtained from single point values and data obtained by MCS. This is because of input variable employed for each models. For example, when MOE obtained by single point data, IR assumed 100 g/day. However, this value in MCS expected 39 ± 3 g/day. This difference will affect final output, remarkably.

Uncertainties are inherent in evaluation of risk, which could refer to toxicity assessment and exposure. Although MCS was applied to assess the uncertainties and its impact on risk estimation, there were still other uncertainties during the processes of risk characterization, especially for the variables determined by sensitivity analysis. Because of the limited dose–response data on carcinogenic compounds, the risk assessment of PAHs mixture for human remains changeable. Herein, the TEFs were used to convert PAHs concentrations to BaPeq level. These values have acquired from animal studies. It was found that TEF values obtained from experimental data always led to in different TEF values, especially for high weight PAHs. Specific-chemical parameters such as CSF and $BMDL_{10}$ were obtained from animal studies. Uncertainties may occurred during the extrapolation of animal data to human. In addition, probability distributions of BW was obtained from previous published studies, which can results in uncertainty (Wu et al., 2011).

Similar to our findings, in 2016, Li and co-workers exhibited that concentration of PAHs, ED, CSF and IR are important variables that sensitively correlated with ILCR (Li et al., 2016a). The results were consistent with the report of Xia et al. (2010) which estimated the carcinogenic risk of PAHs in twenty-five kinds of seven categories of food in China. They showed that CSF and ED are the most important factors in health risk assessment. Several studies reported that ED was the sensitive parameter in the risk assessment (Wu et al., 2011; Yang et al., 2014, 2015). Another study showed that concentration of PAHs

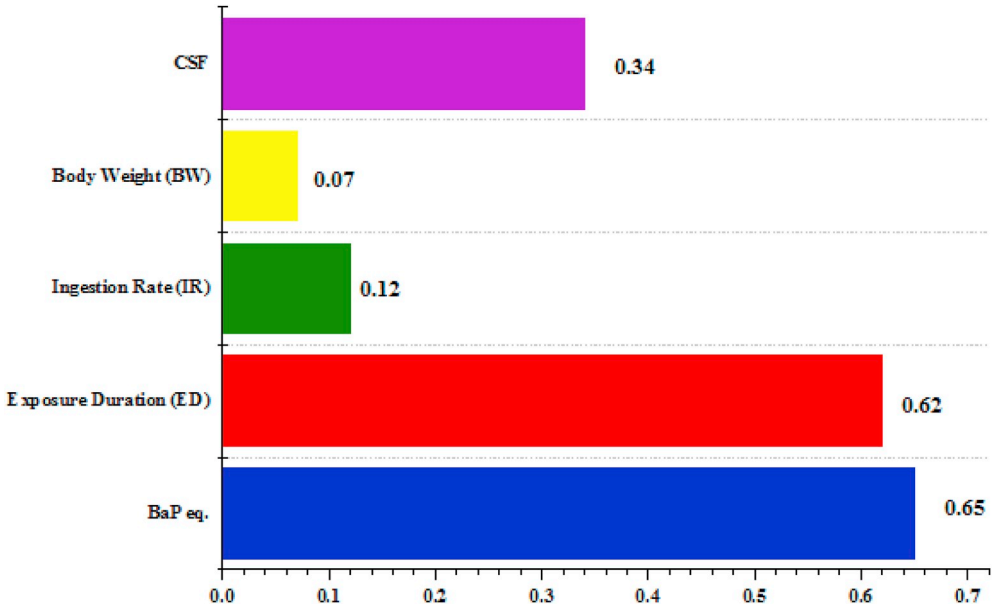

Fig. 6. Influential parameters in ILCR (Baby food).

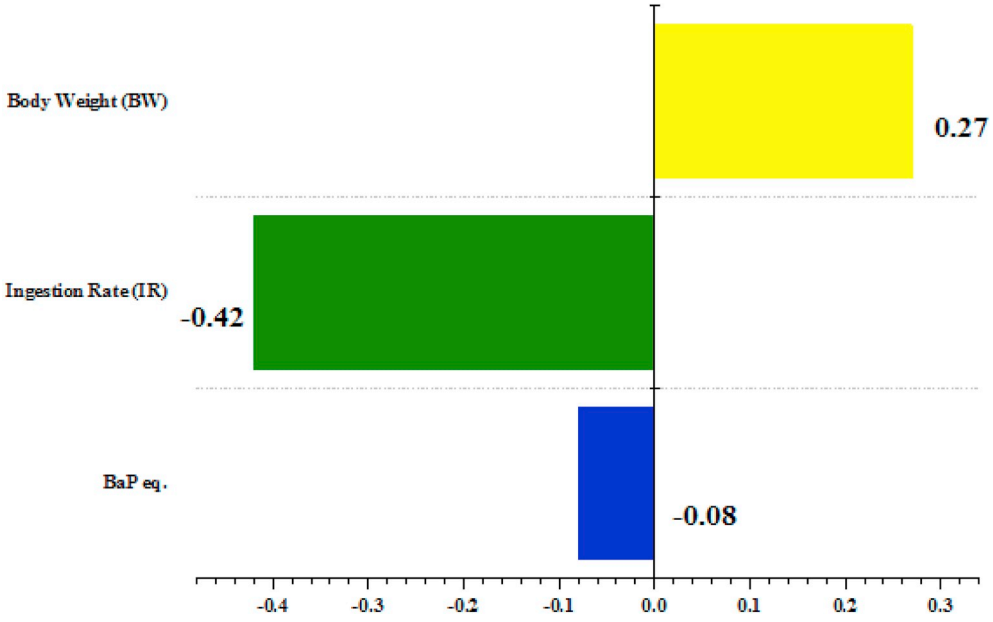

Fig. 7. Influential parameters in MOE (Milk powder).

and ED are the most influential variable in quantitative evaluation of carcinogenic potential of PAHs (Yang et al., 2015). Hence, based on the sensitivity results, we can enhance the accuracy of the risk assessment by improving the accuracy of Σ BaP eq., ED, CSF and IR.

5. Conclusions

In the current study, the levels of PAH4 were determined in commonly used brands of infant formula, follow-on formula, and baby foods in Iran, using GC-MS. In addition, risk assessment for infants and toddlers performed, with the help of incremental lifetime cancer risk (ILCR) and margin of exposure (MOE) formulas in Monte Carlo Simulation (MCS) method. The results of MCS showed that there is no serious risk for infants and toddlers by ingestion of infant formula, follow-on formula and baby foods. Furthermore, based on the sensitivity results in this study, we found that Σ BaP eq., ED, CSF and IR are the most influential factors in risk assessment. Due to presence of PAH4 in analyzed brands, particular attention is required. Presence of PAHs in infant formulae and follow-on formulae products depend both on environmental pollution of the area in which milk was produced and conditions during processing. Although production of PAHs requires temperatures of 500–700 °C, PAHs can be produced at 100–150 °C. Packaging material is another factor from which contents can become contaminated by PAHs. It is recommended to select non-polluted raw material and establish good manufacturing practice to minimized contamination of final products. Because of low sample size in our study, further research on PAHs content in such products is still needed to continuously control the exposure of infants and babies to these compounds.

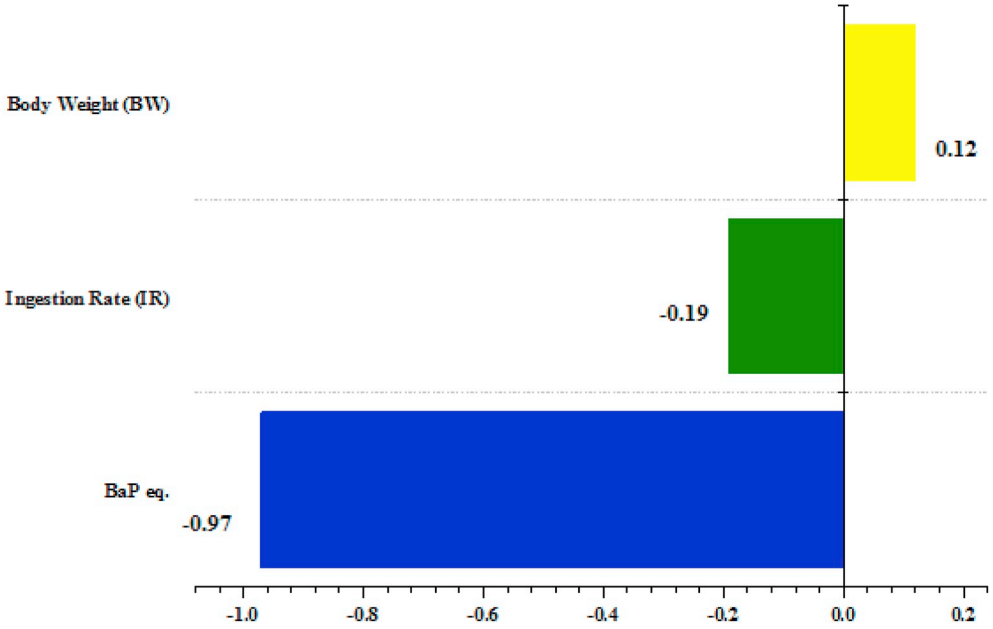

Fig. 8. Influential parameters in MOE (Baby food).

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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References

Acharya, N., Gautam, B., Subbiah, S., Rogge, M.M., Anderson, T.A., Gao, W., 2019. Polycyclic aromatic hydrocarbons in breast milk of obese vs normal women: infant exposure and risk assessment. Science of Sci Total Environ 668, 658–667.

Amirdivani, S., Khorshidian, N., Ghobadi Dana, M., Mohammadi, R., Mortazavian, A.M., Quiterio de Souza, S.L., Barbosa Rocha, H., Raices, R., 2019. Polycyclic aromatic hydrocarbons in milk and dairy products. Int J Dairy Technol 72, 120–131.

Bacigalupo, C., Hale, B., 2012. Human health risks of Pb and as exposure via consumption of home garden vegetables and incidental soil and dust ingestion: a probabilistic screening tool. Sci. Total Environ. 423, 27–38.

Bansal, V., Kim, K.-H., 2015. Review of PAH contamination in food products and their health hazards. Environ. Int. 84, 26–38.

Belo, R.F.C., Pissinatti, R., de Souza, S.V.C., Junqueira, R.G., 2017. Evaluating matrix effects in the analysis of polycyclic aromatic hydrocarbons from food: can these interferences Be neglected for isotope dilution? Food Anal Methods 10, 1488–1499.

Benford, D., DiNovi, M., Setzer, R.W., 2010. Application of the margin-of-exposure (MoE) approach to substances in food that are genotoxic and carcinogenic eg: benzo [a] pyrene and polycyclic aromatic hydrocarbons. Food Chem. Toxicol. 48, S42–S48.

Bogusz, M.J., El Hajj, S.A., Ehaideb, Z., Hassan, H., Al-Tufail, M., 2004. Rapid determination of benzo (a) pyrene in olive oil samples with solid-phase extraction and low-pressure, wide-bore gas chromatography–mass spectrometry and fast liquid chromatography with fluorescence detection. J Chromatogr A 1026, 1–7.

Cho, H.-K., Shin, H.-S., 2012. Evaluation of polycyclic aromatic hydrocarbon contents and risk assessment for infant formula in Korea. Food Sci Biotechnol 21, 1329–1334.

Choi, H., Song, W.-m., Wang, M., Sram, R.J., Zhang, B., 2019. Benzo [a] pyrene is associated with dysregulated myelo-lymphoid hematopoiesis in asthmatic children. Environ. Int. 128, 218–232.

Ciecierska, M., Obiedziński, M., 2010. Polycyclic aromatic hydrocarbons in infant formulae, follow-on formulae and baby foods available in the Polish market. Food Control 21, 1166–1172.

Clark, K.E., David, R.M., Guinn, R., Kramarz, K.W., Lampi, M.A., Staples, C.A., 2011. Modeling human exposure to phthalate esters: a comparison of indirect and biomonitoring estimation methods. Hum Ecol Risk Assess 17, 923–965.

Commission, E., 2015. Commission Regulation (EU) 2015/1125 of 10 July 2015 amending Regulation (EC) No 1881/2006 as regards maximum levels for polycyclic aromatic hydrocarbons in Katsuobushi (dried bonito) and certain smoked Baltic herring (Text with EEA relevance), off. J. Eur Union L. 184, 7–10.

de Lima, R.F., Dionello, R.G., Peralba, M.d.C.R., Barrionuevo, S., Radunz, L.L., Júnior, F.W.R., 2017. PAHs in corn grains submitted to drying with firewood. Food Chem. 215, 165–170.

EFSA, 2005. Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. ESPA. J. 3 (282), 2–31.

Fakhri, Y., Saha, N., Ghanbari, S., Rasouli, M., Miri, A., Avazpour, M., Rahimizadeh, A., Riahi, S.-M., Ghaderpoori, M., Keramati, H., 2018. Carcinogenic and non-carcinogenic health risks of metal (oid) s in tap water from Ilam city, Iran. Food Chem. Toxicol. 118, 204–211.

Falcón, M.G., Amigo, S.G., Yusty, M.L., de Alda Villaizan, M.L., Lozano, J.S., 1996. Enrichment of benzo [a] pyrene in smoked food products and determination by high-performance liquid chromatography-fluorescence detection. J Chromatogr A 753, 207–215.

Fathabad, A.E., Shariatifar, N., Moazzen, M., Nazmara, S., Fakhri, Y., Alimohammadi, M., Azari, A., Khaneghah, A.M., 2018. Determination of heavy metal content of processed fruit products from Tehran's market using ICP-OES: a risk assessment study. Food Chem. Toxicol. 115, 436–446.

FSA (Food Standards Agency), 2006. PAHs in baby foods and infant formulae. Food. Survill. Info. Sheet. 09/06.

García-Falcón, M.S., Cancho-Grande, B., Simal-Gándara, J., 2005. Minimal clean-up and rapid determination of polycyclic aromatic hydrocarbons in instant coffee. Food Chem. 90, 643–647.

García Londoño, V.A., Reynoso, C.M., Resnik, S., 2017. Polycyclic aromatic hydrocarbons in milk powders marketed in Uruguay. Food Addit. Contam. Part B Surveill 10, 284–291.

Huo, X., Wu, Y., Xu, L., Zeng, X., Qin, Q., Xu, X., 2019. Maternal urinary metabolites of PAHs and its association with adverse birth outcomes in an intensive e-waste recycling area. Environ. Pollut. 245, 453–461.

Iwegbue, C.M., Ededeme, J.N., Tesi, G.O., Bassey, F.I., Martincigh, B.S., Nwajei, G.E., 2014. Polycyclic aromatic hydrocarbon concentrations in commercially available infant formulae in Nigeria: estimation of dietary intakes and risk assessment. Food Chem. Toxicol. 72, 221–227.

Keramati, H., Ghorbani, R., Fakhri, Y., Khaneghah, A.M., Conti, G.O., Ferrante, M., Ghaderpoori, M., Taghavi, M., Baninameh, Z., Bay, A., 2018. Radon 222 in drinking water resources of Iran: a systematic review, meta-analysis and probabilistic risk assessment (Monte Carlo simulation). Food Chem. Toxicol. 115, 460–469.

Kishikawa, N., Wada, M., Kuroda, N., Akiyama, S., Nakashima, K., 2003. Determination of polycyclic aromatic hydrocarbons in milk samples by high-performance liquid chromatography with fluorescence detection. J. Chromatogr. B 789, 257–264.

Lee, J., Jeong, J.-H., Park, S., Lee, K.-G., 2018. Monitoring and risk assessment of polycyclic aromatic hydrocarbons (PAHs) in processed foods and their raw materials. Food Control 92, 286–292.

Li, G., Wu, S., Wang, L., Akoh, C.C., 2016a. Concentration, dietary exposure and health risk estimation of polycyclic aromatic hydrocarbons (PAHs) in youtiao, a Chinese traditional fried food. Food Control 59, 328–336.

Li, J., Dong, H., Li, X., Han, B., Zhu, C., Zhang, D., 2016b. Quantitatively assessing the health risk of exposure to PAHs from intake of smoked meats. Ecotoxicol. Environ. Saf. 124, 91–95.

Moret, S., Conte, L.S., 2002. A rapid method for polycyclic aromatic hydrocarbon determination in vegetable oils. J. Sep. Sci. 25, 96–100.

Morisset, T., Ramirez-Martinez, A., Wesolek, N., Roudot, A.-C., 2013. Probabilistic mercury multimedia exposure assessment in small children and risk assessment. Environ. Int. 59, 431–441.

Moudgil, P., Bedi, J.S., Aulakh, R.S., Gill, J.P.S., Kumar, A., 2019. Validation of HPLC multi-residue method for determination of fluoroquinolones, tetracycline, sulphonamides and chloramphenicol residues in bovine milk. Food Anal Methods 12, 338–346.

Nepalia, A., Singh, A., Mathur, N., Pareek, S., 2017. Baby foods can have toxic side effects: a review. Asian J Sci Tech 8, 4386–4393.

Nie, J., Shi, J., Duan, X., Wang, B., Huang, N., Zhao, X., 2014. Health risk assessment of dietary exposure to polycyclic aromatic hydrocarbons in Taiyuan, China. J. Environ. Sci. 26, 432–439.

Nyiri, Z., Novák, M., Bodai, Z., Petrovics, N., Eke, Z., 2017. Determination of polycyclic aromatic hydrocarbons in infant formula using solid state urea clathrate formation with gas chromatography–tandem mass spectrometry. Talanta 174, 214–220.

Oh, J.-Y., Choi, S.-D., Kwon, H.-O., Lee, S.-E., 2016. Leaching of polycyclic aromatic hydrocarbons (PAHs) from industrial wastewater sludge by ultrasonic treatment. Ultrason. Sonochem. 33, 61–66.

Purcaro, G., Moret, S., Conte, L.S., 2013. Overview on polycyclic aromatic hydrocarbons: occurrence, legislation and innovative determination in foods. Talanta 105, 292–305.

Rahmani, J., Alipour, S., Miri, A., Fakhri, Y., Riahi, S.-M., Keramati, H., Moradi, M., Amanidaz, N., Pouya, R.H., Bahmani, Z., 2018. The prevalence of aflatoxin M1 in milk of Middle East region: a systematic review, meta-analysis and probabilistic health risk assessment. Food Chem. Toxicol. 118, 653–666.

Razzaghi, N., Ziarati, P., Rastegar, H., Shoeibi, S., Amirahmadi, M., Conti, G.O., Ferrante, M., Fakhri, Y., Khaneghah, A.M., 2018. The concentration and probabilistic health risk assessment of pesticide residues in commercially available olive oils in Iran. Food Chem. Toxicol. 120, 32–40.

Rengarajan, T., Rajendran, P., Nandakumar, N., Lokeshkumar, B., Rajendran, P., Nishigaki, I., 2015. Exposure to polycyclic aromatic hydrocarbons with special focus on cancer. Asian Pac J Trop Biomed 5, 182–189.

Rey-Salgueiro, L., García-Falcón, M.S., Martínez-Carballo, E., González-Barreiro, C., Simal-Gándara, J., 2008. The use of manures for detection and quantification of polycyclic aromatic hydrocarbons and 3-hydroxybenzo [a] pyrene in animal husbandry. Sci. Total Environ. 406, 279–286.

Rey-Salgueiro, L., Martínez-Carballo, E., García-Falcón, M.S., González-Barreiro, C., Simal-Gándara, J., 2009. Occurrence of polycyclic aromatic hydrocarbons and their hydroxylated metabolites in infant foods. Food Chem. 115, 814–819.

Rozentale, I., Zacs, D., Perkons, I., Bartkevics, V., 2017. A comparison of gas chromatography coupled to tandem quadrupole mass spectrometry and high-resolution sector mass spectrometry for sensitive determination of polycyclic aromatic hydrocarbons (PAHs) in cereal products. Food Chem. 221, 1291–1297.

Santonicola, S., Albrizio, S., Murru, N., Ferrante, M.C., Mercogliano, R., 2017a. Study on the occurrence of polycyclic aromatic hydrocarbons in milk and meat/fish based baby food available in Italy. Chemosphere 184, 467–472.

Santonicola, S., De Felice, A., Cobellis, L., Passariello, N., Peluso, A., Murru, N., Ferrante, M.C., Mercogliano, R., 2017b. Comparative study on the occurrence of polycyclic aromatic hydrocarbons in breast milk and infant formula and risk assessment. Chemosphere 175, 383–390.

Shahrbabki, P.E., Hajimohammadi, B., Shoeibi, S., Elmi, M., Yousefzadeh, A., Conti, G.O., Ferrante, M., Amirahmadi, M., Fakhri, Y., Khaneghah, A.M., 2018. Probabilistic non-carcinogenic and carcinogenic risk assessments (Monte Carlo simulation method) of the measured acrylamide content in Tah-dig using QuEChERS extraction and UHPLC-MS/MS. Food Chem. Toxicol. 118, 361–370.

Sirot, V., Riviere, G., Leconte, S., Vin, K., Traore, T., Jean, J., Carne, G., Gorecki, S., Veyrand, B., Marchand, P., 2019. French infant total diet study: dietary exposure to heat-induced compounds (acrylamide, furan and polycyclic aromatic hydrocarbons) and associated health risks. Food Chem. Toxicol. 130, 308–316.

Soceanu, A., Dobrinas, S., Popescu, V., 2016. Polycyclic aromatic hydrocarbons in Romanian baby foods and fruits. Polycycl. Aromat. Comp. 36, 364–375.

Srivastava, P., Sreekrishnan, T., Nema, A., 2017. Human health risk assessment and PAHs in a stretch of river Ganges near Kanpur. Environ. Monit. Assess. 189, 445.

Suparmi, S., Widiastuti, D., Wesseling, S., Rietjens, I.M., 2018. Natural occurrence of genotoxic and carcinogenic alkenylbenzenes in Indonesian jamu and evaluation of consumer risks. Food Chem. Toxicol. 118, 53–67.

Szelewski, M., 2005. Synchronous SIM/Scan Low-Level PAH Analysis Using the Agilent

Technologies 6890/5975 Inert GC/MSD. Agilent Technologies, publication.
Taghizadeh, S.F., Davarynejad, G., Asili, J., Nemati, S.H., Rezaee, R., Goumenou, M., Tsatsakis, A.M., Karimi, G., 2017. Health risk assessment of heavy metals via dietary intake of five pistachio (Pistacia vera L.) cultivars collected from different geographical sites of Iran. Food Chem. Toxicol. 107, 99–107.
Taghizadeh, S.F., Rezaee, R., Davarynejad, G., Asili, J., Nemati, S.H., Goumenou, M., Tsakiris, I., Tsatsakis, A.M., Shirani, K., Karimi, G., 2018. Risk assessment of exposure to aflatoxin B1 and ochratoxin A through consumption of different Pistachio (Pistacia Vera L.) cultivars collected from four geographical regions of Iran. Environ. Toxicol. Pharmacol. 61, 61–66.
Tian, K., Bao, H., Zhang, X., Shi, T., Liu, X., Wu, F., 2018. Residuals, bioaccessibility and health risk assessment of PAHs in winter wheat grains from areas influenced by coal combustion in China. Sci. Total Environ. 618, 777–784.
Wang, M., Cheng, C., Liu, C., Yang, Y., 2018. Hollow fiber supported ionic liquids liquid-phase micro-extraction followed by high-performance liquid chromatography for the determination of polycyclic aromatic hydrocarbons in milk samples. J. Chromatogr. Sci. 56, 74–80.
Wang, S., Suh, J.H., Hung, W.-L., Zheng, X., Wang, Y., Ho, C.-T., 2018. Use of UHPLC-TripleQ with synthetic standards to profile anti-inflammatory hydroxycinnamic acid amides in root barks and leaves of Lycium barbarum. J. Food Drug Anal. 26, 572–582.
Watanabe, K.H., Djordjevic, M.V., Stellman, S.D., Toccalino, P.L., Austin, D.F., Pankow, J.F., 2009. Incremental lifetime cancer risks computed for benzo [a] pyrene and two tobacco-specific N-nitrosamines in mainstream cigarette smoke compared with lung cancer risks derived from epidemiologic data. Regul. Toxicol. Pharmacol. 55, 123–133.
Wu, B., Zhang, Y., Zhang, X.-X., Cheng, S.-P., 2011. Health risk assessment of polycyclic aromatic hydrocarbons in the source water and drinking water of China: quantitative analysis based on published monitoring data. Sci. Total Environ. 410, 112–118.
Xia, Z., Duan, X., Tao, S., Qiu, W., Liu, D., Wang, Y., Wei, S., Wang, B., Jiang, Q., Lu, B., 2013. Pollution level, inhalation exposure and lung cancer risk of ambient atmospheric polycyclic aromatic hydrocarbons (PAHs) in Taiyuan, China. Environ. Pollut. 173, 150–156.
Xia, Z., Duan, X., Qiu, W., Liu, D., Wang, B., Tao, S., Jiang, Q., Lu, B., Song, Y., Hu, X., 2010. Health risk assessment on dietary exposure to polycyclic aromatic hydrocarbons (PAHs) in Taiyuan, China. Sci. Total Environ. 408, 5331–5337.
Yang, W., Lang, Y., Li, G., 2014. Cancer risk of polycyclic aromatic hydrocarbons (PAHs) in the soils from Jiaozhou Bay wetland. Chemosphere 112, 289–295.
Yang, W., Lang, Y.-H., Bai, J., Li, Z.-Y., 2015. Quantitative evaluation of carcinogenic and non carcinogenic potential for PAHs in coastal wetland soils of China. Ecol. Eng. 74, 117–124.
Yebra-Pimentel, I., Fernández-González, R., Martínez-Carballo, E., Simal-Gándara, J., 2015. A critical review about the health risk assessment of PAHs and their metabolites in foods. Crit. Rev. Food Sci. Nutr. 55, 1383–1405.
Yousefi, M., Shemshadi, G., Khorshidian, N., Ghasemzadeh-Mohammadi, V., Fakhri, Y., Hosseini, H., Khaneghah, A.M., 2018. Polycyclic aromatic hydrocarbons (PAHs) content of edible vegetable oils in Iran: a risk assessment study. Food Chem. Toxicol. 118, 480–489.
Zelinkova, Z., Wenzl, T., 2015. The occurrence of 16 EPA PAHs in food–a review. Polycycl. Aromat. Comp. 35, 248–284.
Zhou, j., Yan, Y., Bai, Z., Hu, Y., Zhang, j., Zhang, N., 2011. Health risk assessment of personal inhalation exposure to volatile organic compounds in Tianjin, China. Sci. Total Environ. 409, 452–459.