PAPER

HUMAN HEALTH RISK ASSESSMENT OF ORGANOCHLORINE COMPOUNDS ASSOCIATED WITH RAW MILK CONSUMPTION IN A ROMANIAN INDUSTRIAL AREA

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ABSTRACT

Dietary exposure to organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), generically named organochlorine compounds (OCCs), now represents a significant health risk for humans due to their endocrine-disrupting and carcinogenic effects. To assess the potential health risk associated with raw milk consumption, 10 milk samples were collected from a local market in the Baia-Mare industrial area, Romania. The concentrations of OCPs and PCB congeners in these samples were determined by capillary gas chromatography with electron-capture detection, after liquid–liquid extraction. In all samples, the OCCs were below the maximum admitted concentrations set by European legislation. The predominant compounds were 4,4'-DDE (11.5 ng/g lipid wt.), β-HCH (10.1 ng/g lipid wt.) and PCB180 (5.08 ng/g lipid wt.). Exposure assessment through milk consumption was performed for male, female and children by calculating the estimated daily intakes (EDIs) and the hazard indices (HIs) for non-carcinogenic effects. The obtained EDIs were lower than the acceptable daily intake values, and HIs were far below 1, indicating no potential health risk for the investigated population.

Keywords: health risk assessment, OCPs, PCBs, raw milk

1. INTRODUCTION

Foods of animal origin play an essential role in human nutrition. Milk and dairy products are a source of micro- and macro-elements and active compounds that play an important role in nutrition and health (CADAR *et al*., 2015). The microbial and chemical contamination of raw milk during animal feed production, dairy processing or packaging is of great concern for public health, especially for products purchased from local producers.

The primary chemical contaminants in milk and dairy products are antibiotics, anthelmintic drugs, hormones, pesticides, heavy metals, mycotoxins, nitrites, etc. (KHANIKI, 2007; SELIM *et al*., 2015). Organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) are persistent in the environment and have the potential to bioaccumulate along the food chain, and this may cause adverse health effects (TSAKIRIS *et al*., 2015; YU *et al*., 2011). Most OCPs have endocrine-disrupting effects and can cause hepatotoxicity, immunotoxicity and developmental abnormalities as well as have neurobehavioral effects (MARTINS *et al*., 2013). Despite their international ban starting from the 1980s, they are still detected in the environment, food, biota and humans (HENRÍQUEZ-HERNÁNDEZ *et al*., 2017). The International Agency for Research on Cancer (IARC) has classified most of the OCPs as possibly carcinogenic to humans (group 2B) and "dioxin-like" PCB congeners as carcinogenic to humans (group 1) (KLINCIC *et al*., 2016).

Bioaccumulation of OCCs through the food chain makes foods of animal origin the main source of human exposure to these contaminants (CASPERSEN *et al*., 2016). The exposure of human organisms to environmental contaminants, through food, cannot be avoided, and this can lead to acute (short-term exposure) or chronic (long-term exposure) effects. The human risk assessment can be based on deterministic approaches by comparing it to a threshold toxicity value (CERNA *et al*., 2016). Following the banning of OCCs, the concentrations of OCCs in foodstuff decreased significantly (LI, 1999). There are several papers presenting the level of pesticides in milk and dairy products (SANTOS *et al*., 2015; SANTOS *et al*., 2006; LUZARDO *et al*., 2012; AVANCINI *et al*., 2013; DETI *et al*., 2014) all over the world. Also, there are papers on the human health risks associated with various pesticides in foodstuff (ZHANG *et al*., 2017; CUI *et al*., 2015; LEI *et al*., 2015; ZHAO *et al*., 2014). However, there is only limited information on health risk from pesticides in milk and dairy products (BEDI *et al*., 2015; WITZAK *et al*., 2016).

The aim of this study was to establish the level of 19 OCPs and 7 PCBs in raw milk collected from a local market in Baia Mare city, North Western Romania, and to assess the risk associated with raw milk consumption for the local children and adults according to gender (male, female).

2.MATERIALS AND METHODS

2.1. Sampling

A number of 10 raw cow milk samples were purchased from a local market in Baia Mare city, NW Romania, during 2016. The cow milk is widely consumed by the local inhabitants. Samples were collected in chemical-free glass bottles with Teflon seals and frozen at -20°C until chemical analysis according to the procedure described by HECK *et al*. (2007).

2.2. Reagents, standard solution and CRMs

The used solvents (acetonitrile, dichloromethane, ethanol and n-hexane) were of gas chromatography grade (Merck, Germany). Anhydrous sodium sulphate, and Florisil were used after heating overnight at 120°C. Mix standard solution (EN ISO 6468 CERTAN, NE7550) for OCPs and PCBs was purchased from LGC Standards (Germany). The working standard solutions were prepared by diluting accurate volumes of Mix standard solution in dichloromethane. Milk powder certified reference materials (CRMs) purchased from LGC Standards (Germany) - BCR-188 and BCR-450 - were used for the quality control of the results.

2.3. Sample preparation

The extraction and clean-up of milk samples were carried out according to the method described by ENNACEUR *et al.* (2007). The milk samples were thawed at room temperature and homogenized. 20 ml sample was extracted 3 times with a 20/5/1 mixture (v/v/v) of n-hexane/acetonitrile/ethanol. The hexane layers were filtered over anhydrous sodium sulphate, and evaporated to 5 ml. Afterwards, 1 ml was pipetted in a pre-weighed flask and evaporated to dryness. The difference between the final and the initial weight of the empty flask was used to calculate the lipid content of the sample. 4 ml of extract was purified with Florisil and anhydrous sodium sulphate in a chromatographic mini-column. The extract eluted with a 27/3 elution mixture (v/v) of dichloromethane/n-hexane and evaporated to 1 ml, using a EVA-EC1-S sample concentrator (VLM, Germany)

2.4. Sample analysis

In this study the following compounds were determined: α-, β-, γ-, δ-, ε-isomers of hexachlorocyclohexane (expressed as HCHs), 1,1,1-trichloro-2,2-bis-(chlorophenyl)ethane (DDT), 1,1-dichloro-2,2,-bis-(chlorophenyl)ethane (DDD), and dichlorodiphenyl-chloroethylene (DDE), each with their isomers 4,4′- and 2,4′-, expressed as DDTs; aldrin, dieldrin, heptachlor, heptachlor epoxide isomer A, heptachlor epoxide isomer B, α-endosulfan, β-endosulfan, hexachlorobenzene (HCB) and PCB congeners: tri (28), tetra (52), penta (101), hexa (138, 153), hepta (180) and octa (194). In order to separate, detect and quantify the OCCs, an Agilent Technologies 6890N gas chromatography equipped with a 63Ni μ-electron-capture detector (GC-ECD) and an Agilent J&W, DB-1 capillary column (30 m L × 0.32 mm i.d. with film thickness 3.0 μm) were used. Subsequent to extraction and evaporation, 1 μl of purified extract was injected in splitless mode, at 280°C. The GC oven temperature program consists of 4 stages: from 80°C to 196°C (rate 4°C/min, 2 min), from 196°C to 224°C (rate 4°C/min, 2 min), from 224°C to 240°C (rate 4°C/min, 2 min) and from 240°C to 275°C (rate 4°C/min, 2 min). OCCs were identified by comparison of each relative retention time with the calibration standards. Confirmation of compounds was performed using an Agilent Technologies 6890N coupled with 5975B Agilent Technologies quadrupole GC-MS system. For quantification, multi-level calibration curves were created using standard solutions, and good correlations (r^2=0.995) were achieved.

2.5. Human health risk assessment

For estimating long-term exposure through food intake, the average consumption over a period of time and the ratio between the average consumption and the reference values of the contaminant amount (μg/kg body weight) that can be consumed daily over a lifetime without appreciable health risks were considered (LEMOS *et al.*, 2016). The exposure to OCCs through food ingestion was evaluated by estimating the dietary exposure, by calculating the estimated daily intake (EDI) from the amount of analyte found in milk and the daily milk consumption by population. EDI is expressed in μg contaminant/person/day. The risk assessment was evaluated by calculation of hazard indices (HIs), expressed as the ratio between exposure and reference dose. If HI<1, the daily exposure does not have potentially adverse effects on the consumers' health over the lifetime (LEMOS *et al.*, 2016; LI *et al.*, 2015).

3. RESULTS AND DISCUSSIONS

3.1. Organochlorine pesticides in milk samples

The obtained results for both CRMs were in agreement with the certified values. OCPs, 4,4'-DDE and 4,4'-DDT metabolites were found in all investigated milk samples. The most frequently found compounds were 4,4'-DDE (11.5 ng/g lipid wt.), β-HCH (10.1 ng/g lipid wt.) and PCB180 (5.08 ng/g lipid wt.). The concentration range, average and standard deviation along the incidence of OCPs in the investigated milk samples are shown in Table 1.

For statistical purposes, the concentrations below the quantification limit (LQ<0.05 ng/g lipid wt.) were considered equal to 0.5LQ (LE FAOUDER *et al.*, 2007). To compare the found OCP concentrations with the legislative threshold values, the maximum admitted concentrations (MACs) expressed in μg/kg (Order 23, 2007) were converted to ng/g lipid wt., considering a mean lipid wt. of 4% in milk (GEBREMICHAEL *et al.*, 2013). Both the individual and the sum of OCP concentrations were below MACs, according to Romanian legislation (Order 23, 2007). The graphical representation of the sum of HCH, sum of cyclodienes, sum of endosulfans and sum of chloro-diphenyl aliphatic compounds concentrations is shown in Fig. 1.

HCB was detected in 80% of samples, with a maximum value of 4.32 ng/g lipid wt., significantly lower than MAC. Endosulfan (α and/or β isomer) was detected in 90% of investigated samples, in relatively low concentrations. The average concentration of α-endosulfan was lower than β-endosulfan β isomer, in accordance with the higher predilection of β isomer compared to α isomer (TSIPLAKOU *et al.*, 2010). HCH compounds were detected in all the analysed samples. The average concentrations of HCH isomers varied in the following order: β-HCH>γ-HCH>α-HCH>δ-HCH>ε-HCH. The total concentrations of HCHs varied between 3.64 and 37.8 ng/g lipid wt., with average and standard deviation values of 6.53 and 3.55 ng/g lipid wt., respectively.

Compounds from cyclodiene group were detected in all milk samples, except one, but the obtained values were low. The average values ranged in the following order: dieldrin>heptachlor>heptachlor epoxide β>aldrin>heptachlor epoxide α. The concentrations of aldrin and dieldrin were much lower than their corresponding MACs.

Chloro-diphenyl aliphatic compounds were determined in all analysed samples, the highest contents of total DDTs were recorded in samples 8 (29.3 ng/g lipid wt.), 9 (18.4 ng/g lipid wt.) and 1 (17.8 ng/g lipid wt.), and the predominant component was 4,4'-DDE. The lowest value was reported in sample 5 (3.26 ng/g lipid wt.).

Table 1. Range, average and standard deviation values of OCPs in milk samples.

Compound	**Range (ng/g lipid wt.)**	**Average (ng/g lipid wt.)**	**Standard deviation (ng/g lipid wt.)**	**MAC (μg/kg / ng/g lipid wt.)**	**Samples > MAC (%)**	**Incidence (%)**
HCB	<0.05-4.32	2.18	1.61	10*/**250**	0	80
			Hexachlorcyclohexanes (HCH)			
α-HCH	<0.05-6.49	1.65	2.01	4*/**100**	0	90
β-HCH	<0.05-17.4	10.14	5.21	3*/**75**	0	90
γ-HCH (Lindane)	<0.05-7.16	2.92	2.81	8*/**200**	0	90
δ-HCH	0.25-4.34	1.70	1.37	-	-	90
ε-HCH	<0.05-2.41	0.68	0.78	-	-	80
ΣHCHs	3.64-37.8	17.1	10.3	-	-	
			Cyclodienes			
Aldrin	<0.05-1.71	0.63	0.62	6*/**150**	0	70
Dieldrin	<0.05-6.49	2.45	2.04	6*/**150**	0	80
Heptachlor	<0.05-6.25	2.30	1.93	-	-	90
Heptachlor epoxide β	<0.05-2.03	0.94	0.66	-	-	90
Heptachlor epoxide α	<0.05-0.69	0.22	0.23	-	-	80
			Endosulfans			
β-endosulfan	<0.05-1.82	0.57	0.44	-	-	80
α-endosulfan	<0.05-1.27	0.42	0.47	-	-	70
ΣEndosulfan	<0.10-2.63	0.98	0.69	4*/**100****	0	
			Chloro-diphenyl aliphatic compounds			
2,4'-DDE	<0.05-0.13	0.07	0.04	-	-	70
4,4'-DDE	2.93-28.4	11.52	8.15	-	-	100
2,4'-DDD	<0.05-0.48	0.12	0.15	-	-	70
4,4'-DDD	<0.05-0.44	0.13	0.14	-	-	70
2,4'-DDT	<0.05-0.24	0.12	0.08	-	-	80
4,4'-DDT	0.05-3.67	0.58	1.17	-	-	100
ΣDDTs***	3.21-28.9	12.3	7.96	40*/**1000**	0	
ΣOCPs	12.7-68.1	37.1	16.6	**-**	-	

*according to Romanian legislation (Order 23, 2007).
**according to Codex Alimentarius (FAO/WHO, 2006).
***Σ(4,4'-DDE+4,4'-DDD+2,4'-DDT+4,4'-DDT).

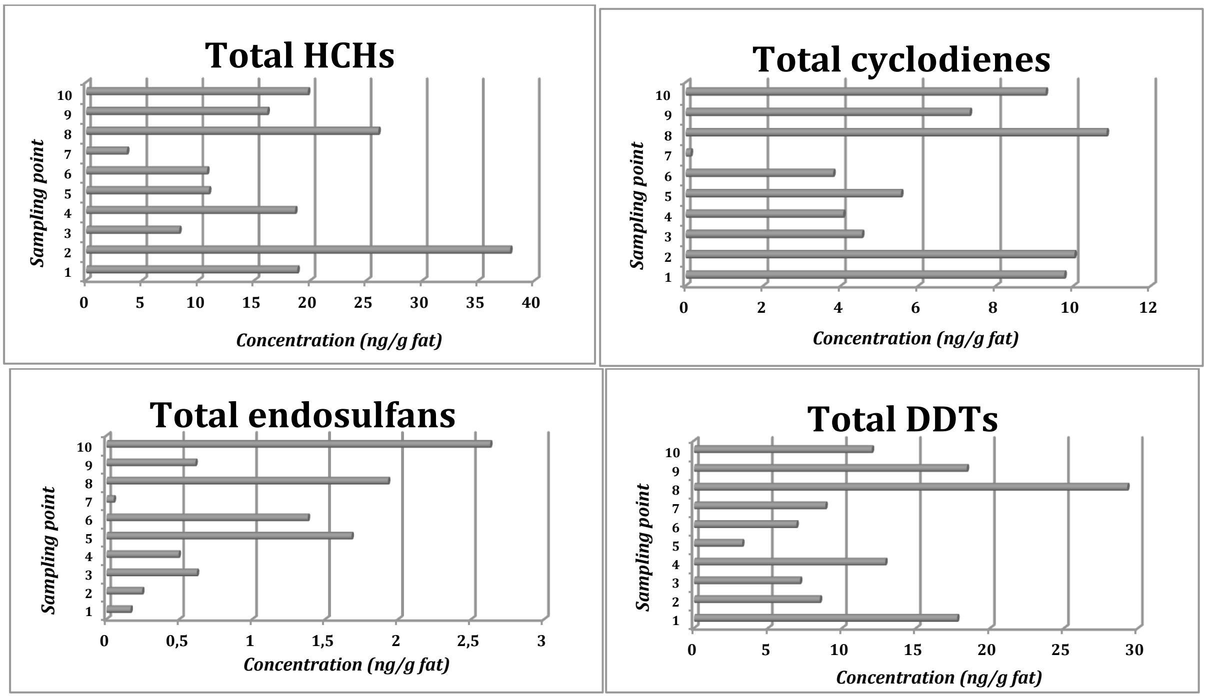

Figure 1. Concentrations of total HCHs, cyclodienes, endosulfans and total DDT (ng/g lipid wt.) in milk samples.

The obtained values for OCPs in milk samples were comparable with those reported by HECK *et al.* (2007) in milk samples consumed in Rio Grande do Sul, Brazil, for HCB, α-HCH, 4,4′-DDE and lower for lindan, aldrin, 2,4′-DDD and 2,4′-DDT. Also, the average values obtained for ΣDDT were comparable with the average values reported in Yugoslavia and Canada and lower than in Egypt, Mexico, Ethiopia, Ghana, India, Tunisia and Iran (GEBREMICHAEL *et al.*, 2013). The obtained average values were comparable with those reported by MICLEAN *et al.* (2011) in milk samples collected in Cluj-Napoca area (Romania), except for β-HCH and β-endosulfan, which were lower, while dieldrin, heptachlor, 4,4′-DDD and 4,4′-DDT were higher.

3.2. Polychlorinated biphenyls in milk samples

PCBs were detected in all samples. The range, average and standard deviation values of PCB concentrations in milk samples are shown in Table 2. The highest contribution to the total PCB content is represented by congener PCB180.
The total concentrations of PCBs (expressed as the sum of the seven congeners: PCB 28, 52, 101, 138, 153, 180 and 194) varied between <0.60 ng/g lipid wt. (sample 7) and 15.3 ng/g lipid wt. (sample 4), with average and standard deviation of 9.12 ng/g lipid wt. and 4.99 ng/g lipid wt., respectively.
In the case of non-dioxin like PCBs, the European Commission set the MAC to 100 ng/g lipid wt. from milk for the sum of the seven PCB congeners (PCB 28, 52, 101, 138, 153, 180, 194) (EFSA, 2005; EC, 2006a,b) and recently set the MAC as 40 ng/g lipid wt. from milk for the sum of six congeners (PCB 28, 52, 101, 138, 153 and 180) (EC, 2011) (PÉREZ *et al.*, 2012). In the analysed milk samples, the MAC was not exceeded.
The contribution of the PCB congeners to the total PCB content in analysed milk samples is shown in Fig. 2.

Table 2. Range, average and standard deviation values of PCBs in milk samples

Compound	Range (ng/g lipid wt.)	Average (ng/g lipid wt.)	Standard deviation (ng/g lipid wt.)	Incidence (%)
PCB28	<0.05-0.44	0.18	0.17	70
PCB52	<0.05-0.23	0.09	0.07	80
PCB101	<0.05-3.71	0.89	1.42	50
PCB138	<0.05-2.26	0.54	0.75	80
PCB153	<0.05-5.37	1.09	1.88	40
PCB180	<0.05-10.4	5.08	3.30	80
PCB194	<0.05-5.32	1.25	2.11	30
ΣPCB*	<0.60-15.3	9.12	4.99	

*ΣPCB – sum of PCB congeners (PCB 28, 52, 101, 138, 153, 180, 194).

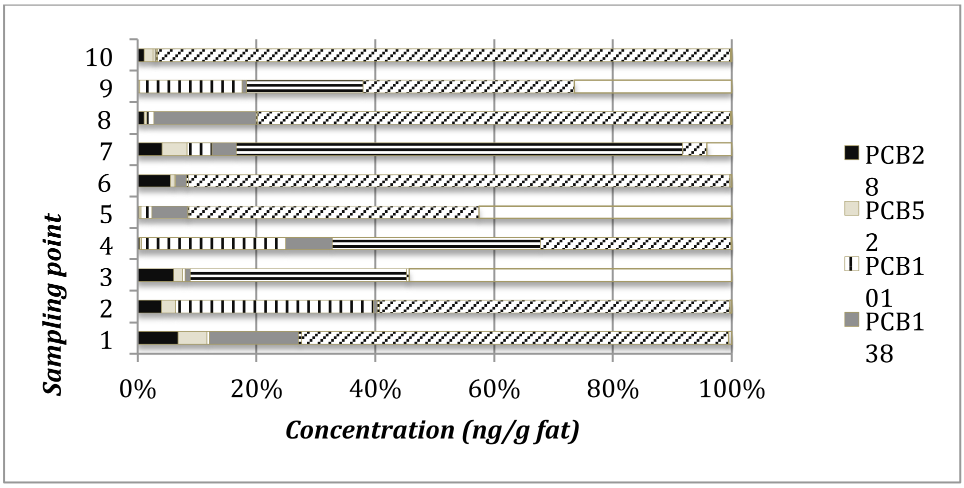

Figure 2. PCB congeners contribution of total PCB content in milk samples.

3.3. Estimated daily intake

In this study, the long-term exposure was assessed by determination of the average intake of OCPs and PCBs through milk consumption for the three population groups - male, female and children - and their comparison with the reference values, namely acceptable daily intake (ADI), set by the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO, 2006).

The daily intake of milk for the three investigated population groups was determined based on milk consumption frequency questionnaires. These questionnaires were filled out by 75 individuals - 55 adults (18-75 years old), among them 28 male, 27 female and 20 children (6-10 years old) - and indicated an average milk daily intake of 300 g milk/person/day for male, 200 g milk/person/day for female and 500 g milk/person/day for children and the average body weight - 75 kg for male, 65 kg for female and 30 kg for children.

The values obtained for the estimated daily intake (EDI) associated with milk consumption are shown in Table 3. In calculations, the pesticides concentrations lower than LQ were considered zero (LUZARDO *et al*., 2012).

Table 3. Average estimated daily intake (EDI) and acceptable daily intake (ADI) of organochlorine compounds (μg/kg bw*/day).

Compound	EDI, μg/kg bw/day			ADI, μg/kg bw/day***
	Female	Male	Children	
Hexachlorbenzene	0.00033	0.00043	0.00181	-
Hexachlorcyclohexanes (HCH)				
α-HCH	0.00034	0.00044	0.00185	-
β-HCH	0.00138	0.00180	0.00748	-
γ-HCH (Lindane)	0.00039	0.00051	0.00213	5
δ-HCH	0.00023	0.00030	0.00124	-
ε-HCH	0.00010	0.00013	0.00056	-
ΣHCH	0.00223	0.00255	0.01207	0.3
Cyclodienes				
Aldrin	0.00011	0.00014	0.00060	0.1
Dieldrin	0.00037	0.00048	0.00199	0.1
Heptachlor	0.00032	0.00041	0.00171	-
Heptachlor epoxide β	0.00013	0.00017	0.00071	-
Heptachlor epoxide α	0.00004	0.00005	0.00020	-
ΣHeptachlor	0.00043	0.00056	0.00232	0.1
Endosulfans				
α-endosulfan	0.00009	0.00011	0.00046	-
β-endosulfan	0.00007	0.00009	0.00038	-
ΣEndosulfans	0.00016	0.00020	0.00084	6
Chloro-diphenyl aliphatic compounds				
2,4'-DDE	0.00001	0.00001	0.00006	-
4,4'-DDE	0.00142	0.00184	0.00768	-
2,4'-DDD	0.00002	0.00003	0.00011	-
4,4'-DDD	0.00002	0.00003	0.00011	-
2,4'-DDT	0.00002	0.00002	0.00009	-
4,4'-DDT	0.00008	0.00009	0.00039	-
ΣDDT**	**0.00154**	**0.00200**	**0.00834**	10
ΣOCPs	**0.00495**	**0.00644**	**0.02682**	-
PCB2013				
PCB28	0.00003	0.00004	0.00017	-
PCB52	0.00001	0.00002	0.00008	-
PCB101	0.00022	0.00028	0.00118	-
PCB138	0.00008	0.00010	0.00043	-
PCB153	0.00035	0.00045	0.00187	-
PCB180	0.00077	0.00100	0.00417	-
PCB194	0.00053	0.00069	0.00286	-
ΣOCCs	**0.00607**	**0.00789**	**0.03287**	-

*bw=body weight.
** 2,4'-DDE + 4,4'-DDE + 2,4'-DDD + 4,4'-DDD + 2,4'-DDT + 4,4'-DDT.
*** EFSA, 2013.

The obtained values for the estimated daily intake of investigated organochlorine compounds, through milk consumption, for adults (male and female) and children, in Baia Mare area were far below ADI values set by the European Food Safety Authority (EFSA), according to Table 3 (EFSA, 2013).

For each investigated analyte, the average estimated daily intake varied in the following order: $EDI_{children}$>EDI_{male}>EDI_{female}, according to the daily milk consumption and body weight. For the investigated children, the EDI value calculated for ΣHeptachlor provides 2.32% from ADI value, set for the sum of these cyclodienes.

The values obtained for EDI of total DDT were below the EFSA recommended value (10 μg/kg bw) and were much lower (4 orders of magnitude). The obtained EDI values for total DDT were comparable (the same order of magnitude) with the values reported in Spain, Poland and China and were lower (with an order of magnitude) than those obtained in Ethiopia, Mexico, Egypt and Iran, through cow milk consumption (GEBREMICHAEL *et al.*, 2013).

The EDIs obtained in this study were comparable with those determined by LUZARDO *et al.* (2012) for adult and child consumers of milk in Spain for hexachlorobenzene, dieldrin, heptachlor and higher (but the same order of magnitude in both studies) for α-, β, γ-, δ-HCH, aldrin, endosulfan, 4,4′-DDT. The average EDI values for total OCPs were comparable in both studies for adults and children.

3.4. Risk assessment

In order to assess the non-carcinogenic risk from exposure to milk through consumption of the three investigated population groups, the HIs were calculated by dividing the EDI values to the US EPA Reference Doses (RfDs) (TSAKIRIS *et al.*, 2015). US EPA provides RfD values only for γ-HCH (0.3 μg/kg bw/day) and 4,4′-DDT (0.5 μg/kg bw/day) (US-EPA, 2006). The obtained values for HIs are shown in Table 4.

Table 4. Hazard indices for lindane and 4,4′-DDT.

Compound	Hazard Index		
	Female	Male	Children
γ-HCH (Lindane)	0.0013	0.0017	0.0071
4,4'-DDT	0.00016	0.00018	0.00078

The values of HIs for lindane and 4,4′-DDT were far below 1, indicating no health risk for the investigated population groups through raw milk consumption, in the studied area.

4. CONCLUSIONS

The tendency of organochlorine compounds to accumulate in fatty tissues, their long persistence and high acute health risk raise concerns about their impact on health due to chronic dietary exposure to low concentrations. This study revealed low dietary intake of organochlorine compounds from milk consumption, in females, males and children. The health risk assessment was calculated based on specific values for the investigated area and the intake of organochlorine pesticides. The specific exposure factors were obtained using questionnaires regarding the structure of the diet for three consecutive days. For each investigated analyte, the average estimated dietary exposure varied in order - $EDI_{children}$>EDI_{men}>EDI_{female} - according to the daily consumption of milk. The average daily intake of organochlorine compounds through milk for the investigated residents exposed to chronic pollution was lower than the reference values, indicating no health risks.

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