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Review

Estimation of daily intake and risk assessment of organophosphorus pesticides based on biomonitoring data – The internal exposure approach

Ioanna Katsikantami[a,b], Claudio Colosio[c], Athanasios Alegakis[b], Manolis N. Tzatzarakis[b], Elena Vakonaki[b], Apostolos K. Rizos[a], Dimosthenis A. Sarigiannis[d,e,f], Aristides M. Tsatsakis[b,*]

[a] Department of Chemistry, University of Crete, Foundation for Research and Technology-Hellas, FORTH-IESL, GR-71003, Heraklion, Crete, Greece
[b] Laboratory of Toxicology, Medical School, University of Crete, GR-71003, Heraklion, Crete, Greece
[c] Department of Occupational and Environmental Health of the University of Milan, International Centre for Rural Health of the University Hospital San Paolo, S. Paolo Hospital Unit, Via San Vigilio 43, 20142 Milan, Italy
[d] Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, Greece
[e] HERACLES Research Centre on the Exposome and Health, Centre for Interdisciplinary Research and Innovation (KEDEK), Aristotle University of Thessaloniki, Greece
[f] Environmental Health Engineering, Institute for Advanced Study IUSS, Pavia, Italy

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ABSTRACT

Human exposure to pesticides can be estimated through different approaches. The approach adopted in this study is based on internal dose measures. Studies published during 2001 and 2017 were collected from PubMed and Scopus databases, filtered and organized. The intake of parent compounds is estimated based on the urinary excretion of different OP metabolites applying a mathematical model previously used for similar purposes. Once defined an Estimated Daily Intake (EDI), risk assessment is performed through comparison with specific guideline values and hazard index (HI) is calculated to assess cumulative health risk. The EDI was expressed as malathion, diazinon, parathion, phorate and dimethoate equivalents. Differences in exposure between pregnant women, general population, children and farmers are highlighted and exposures are presented by country and sampling year. Higher exposure to OPs was calculated for farmers, followed by children whereas pregnant women were less exposed. Median HQ values for children ranged between 0.016 and 0.618, for pregnant women 0.005–0.151, for general population 0.008–0.206 and for farmers 0.009–0.979. Combined exposure to dimethoate and phorate was the worst-case scenario. The annual distribution of the urinary DAPs showed that exposure to OPs since 1998 tends to be stable for both children and adults.

1. Introduction

1.1. Chemical characteristics

Organophosphates are the esters of phosphoric acid and they are produced by the consecutive reaction of phosphoric acid with three alcohols. They are used as solvents, insecticides, flame retardants and plasticizers. Organophosphorus pesticides (OPs) are mainly esters, amides or thiol derivatives of phosphoric, phosphonic, phosphorothionic or phosphonothionic acids and are widely used in agriculture to control insect vectors, in commercial buildings or domestic use in homes and gardens. Most OPs belong to the subgroup organothiophosphates (OTPs) and their functional group is the phosphorothioate P = S bond. Malathion, diazinon, fenthion, dimethoate, phorate and chlorpyriphos are the most widely known OTPs while dichlorvos and glyphosate are oxons (P = O). Many OTPs are converted from thions to oxons which have higher toxicity. This conversion occurs in human body by liver enzymes and in the environment under the influence of oxygen and light. Both oxons and thions are hydrolyzed to less toxic alkyl phosphates and further metabolized before their excretion from

Abbreviations: AChE, acetylcholinesterase; ADHD, attention deficit hyperactivity disorder; ADI, acceptable daily intake; OPs, organophosphorus pesticides; DAPs, dialkyl phosphates; DEAMPY, 2-(diethylamino)-6-methylpyrimidin-4-ol/one; DEP, diethylphosphate; DETP, diethylthiophosphate; DEDTP, diethyldithiophosphate; DMP, dimethyl phosphate; DMDTP, dimethyl dithiophosphate; DMTP, dimethylthiophosphate; EDI, estimated daily intake; EFSA, European Food Safety Authority; FSH, follicle-stimulating hormone; GDM, gestational diabetes mellitus; HQ, hazard quotient; IGT, impaired glucose tolerance; IPCS, International Programme on Chemical Safety; LH, luteinizing hormone; MDA, malathion dicarboxylic acid; MMA, malathion moonocarboxylic acid; MRL, maximum residue level; PNP, paranitrophenol; RfD, reference dose; SD, standard deviation; TCPY, 3,5,6-Trichloro-2-pyridinol; US EPA, United States Environmental Protection Agency

* Corresponding author. Medical School, University of Crete, 71003, Heraklion, Crete, Greece.
E-mail address: tsatsaka@uoc.gr (A.M. Tsatsakis).

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body (US EPA, 2013).

The OP group includes more than 100 compounds according to IPCS INCHEM (International Programme on Chemical Safety) and US EPA (United States Environmental Protection Agency) and they are classified as "Highly toxic" (HT) with oral LD50 values in rats less than 50 mg/kg and "Moderately toxic" (MT) with LD50 values over 50 mg/kg and less than 500 mg/kg (IPCS INCHEM; US EPA, 2013).

1.2. Routes of organophosphate exposure

General population is environmentally exposed to OPs through domestic use of pesticide products and consumption of contaminated drinks and food. Occupationally exposed populations include pesticide industry workers engaged in the production of the active ingredients or in the preparation of formulations and agricultural workers who may be engaged in the preparation and application of the mixtures as part of their different activities including re-entry in previously treated fields and professional applicators. Exposure to pesticides affects also workers engaged in application in public health. The main route of exposure for each population group varies. General population is mainly exposed via ingestion while for occupational exposed group inhalation and skin absorption are the main routes. Indoor workers are exposed mainly via inhalation and less via skin absorption while for outdoor workers the main route is dermal exposure and inhalation to a less extent (less than 10%). The amount of dermal absorption varies with the agents and exposure via eyes is also possible through vapors, dusts or aerosols which can cause even systemic poisoning. OPs toxicity is almost entirely due to inhibition of acetylcholinesterase (AChE), an enzyme at the endings of nerves, resulting in accumulation of acetylcholine causing respiratory, myocardial and neuromuscular transmission impairment in human body (IPCS INCHEM).

When OPs enter human body, they are metabolized to specific and non-specific metabolites through a two-step metabolic pathway (Chambers and Carr, 1995). The non-specific metabolites are dialkylphosphates (DAPs) and are classified to dimethylphosphates (DMPs) and diethylphosphates (DEPs). OPs produce either DEPs or DMPs. DMPs include dimethylphosphate (DMP), dimethylthiophosphate (DMTP) and dimethyldithiophosphate (DMDTP) and DEPs are diethylphosphate (DEP), diethylthiophosphate (DETP) and diethyldithiophosphate (DEDTP). Chlorpyrifos and chlorpyrifos methyl, malathion, diazinon, parathion and methyl parathion have specific metabolites, 3,5,6-Trichloro-2-pyridinol (TCPY), malathion mono carboxylic acid (MMA) and malathion dicarboxylic acid (MDA), 2-Isopropyl-4-methyl-6-hydroxypyrimidine (IMPY) and paranitrophenol (PNP), respectively (Heffernan et al., 2016).

1.3. OPs and pollutant residues in food

There are several published studies which indicate specific foods as source of human exposure to OPs. Even low levels of the compounds in these foods may pose a risk for human health due to their consumption over a lifetime. Olive oil (Tsatsakis et al., 2003), milk products (Tsakiris et al., 2015), fruits and vegetables (Christia et al., 2015; Fosu et al., 2017) can in some cases be contaminated by organophosphate, together with other residues including organochlorine compounds. In particular, fenthion and dimethoate have been detected in both organic and conventional olive oils (Tsatsakis et al., 2003). Conventional olive oil was burdened with higher levels of both pesticides (range for fenthion and dimethoate, 122.2–170.2 ng/g and 22.6–27.1 ng/g, respectively for sequential years), but also in organic oil traces of pesticides can be detected (range for fenthion and dimethoate, 3.5–21.5 ng/g and 1.0–9.8 ng/g, respectively). In a recently published study in Ghana (2010–2012), 3483 samples of foods and vegetables were analyzed for organophosphates, organochlorines and synthetic pyrethroids (Fosu et al., 2017). Regarding OPs, dimethoate and pirimiphos-methyl were detected in all collected food samples except for cauliflower and squash, respectively, whereas chlorpyrifos and fenitrothion residues were detected in all samples. Pesticide residues have also been detected in fruit samples (peaches, grapes, bananas, apples, pears and strawberries) from different regions of Greece (Christia et al., 2015). Diazinon, dimethoate, disulfoton sulfone, malaoxon, metamidophos, paraoxon-methyl, phosalone, phoxim and pyrazophos were detected in all fruit samples. In most the detected concentrations were below the Maximum Residue Limits (MRLs) values established in EU. According to the origin of each fruit, geographically close regions had similar residue patterns reflecting similar pest protection requirements and pesticide application. Pesticides in peaches and pears were equally detectable in both peel and flesh of the fruits, whereas in apples they were mainly on their peel.

1.4. Pesticides in the indoor environment

Except for food, air and dust have been proved to be significant sources of pesticides due to their presence in the indoor environment. Bradman and co-authors (Bradman et al., 2007) studied the presence of eleven OPs in houses of farmworkers in various matrices including house dust, indoor and outdoor air but also various surfaces, toys, cotton socks and union suits. Chlorpyrifos, diazinon and malathion were detected in all matrices whereas dichlorvos was detected in indoor and outdoor air and in surface wipe. Acephate and fonofos were detected only in toy wipe, dimethoate in cotton socks, phosmet in union suits while aziphos-methyl, chlorpyriphos oxon and methidathion were not detectable at any matrix. All matrices were contaminated with at least three (house dust) and maximum five OPs (toy wipe). This particular research, detected also pesticide residues in infant formulas and food of toddlers possibly originated from children's hands or from contaminated indoor dusts.

Human exposure to pesticides can be estimated through different approaches. The so called "external exposure approach" provides estimates based only on the presence of agrochemicals in environmental matrices (de Gavelle et al., 2016; Curl et al., 2015; Melnyk et al., 2014). Risk assessment is performed through comparison with MRLs. The limitations of this approach are the different dietary habits among individuals and the multiple sources of exposure to pesticides, which significantly affect the real intake. Risk assessment can be performed only through the definition of a Theoretical Maximum Daily Intake (TMDI). Exposure can be more reliably estimated considering contaminants' concentration in different foods and drinks, and estimating the intake based on existing data on the typical diet followed by the population under evaluation. This approach can bring to the definition of an Estimated Daily Intake (EDI), which might be refined considering also the edible portion of each food. A limit of this approach is that not always detailed data on national/local diets are available. A third approach, only seldom adopted by researchers, is estimating the intake based on internal dose measures (the "internal dose approach"). This is the approach adopted in this study in which we have estimated based on the urinary excretion of different OP metabolites, the intake of parent compounds based on a mathematical model previously used for similar purposes (Dewalque et al., 2014; Katsikantami et al., 2016; Myridakis et al., 2016). Once defined an Estimated Daily Intake (EDI), risk assessment is performed through comparison with specific guideline values and hazard index (HI) is calculated to assess cumulative health risk. Differences in exposure between pregnant women, general population, children and farmers are highlighted and exposures are presented by country and sampling year.

2. Methods

2.1. Study selection criteria

PubMed and Scopus databases were searched using the keywords "organophosphosphate" AND "biomonitoring". Out of the 1380 results,

1048 articles were selected based on criteria which were automatically applied through database filters and included journal article types, full text available, articles written in English and published during 2001 and the first trimester of 2017. Duplicates were removed and records were screened by title to meet the requirements for this study. Articles for flame retardants, environmental monitoring, method development and review studies were eliminated and in total 166 results were finally accepted. The same methodology was applied for the combinations of the keywords "DAPs", "dialkylphosphate" and "toxicity" from which 22 articles were finally obtained.

2.2. Data collection process

The criteria to include a biomonitoring study in the EDI calculation were to present mean or median values of all measured DAPs and to give information about the studied population. The number of the studied population group, gender, age, the examined biological matrices, the detected compounds and their concentrations and statistical associations (positive, negative or no associations) with adverse health effects were registered. Data were organized by population group, year of sampling and country. In total, 37 studies conducted in 14 countries all over the world during 1998–2015 were included in the present analysis. More specifically, 13 studies for children (5103 participants), 13 studies for pregnant women (4015 participants), 5 studies for farmers (540 participants) and 6 studies in general population (9480 participants).

2.3. Calculation of estimated daily intake and hazard index

Human exposure to pesticides is conventionally estimated based on monitoring of pesticide residues in environmental matrices, food and vegetables (de Gavelle et al., 2016; Curl et al., 2015; Melnyk et al., 2014). A mathematical model (Equation (1)) is used to convert the determined pesticides residues in certain foods to EDI taking into consideration the rate of their daily consumption (Gad Alla et al., 2015).

$$EDI\left(\frac{\frac{\mu g}{kg\ bw}}{d}\right) = \sum RL_i\left(\frac{\mu g}{kg}\right) \times F_i\left(\frac{kg}{d}\right) \div BW\,(kg\ bw) \quad (1)$$

RL_i: pesticide residue level; F_i: food consumption rate; BW: body weight.

Most studies on biomonitoring of pesticides are presenting concentrations of biomarkers in biological matrices. However, pesticide regulation, namely JMPR and European Commission, refers to Acceptable Daily Intake (ADI) and Reference Dose (RfD) values expressed as μg/kg bw/day (Table 1). In the present study, an effort was made to estimate the EDI of OPs based on existing biomonitoring data. Similar efforts have already been published (Dewalque et al., 2014; Katsikantami et al., 2016; Myridakis et al., 2016; Payne-Sturges et al., 2009). For the calculation of EDI based on biomonitoring data a commonly used toxicokinetic model (Equation (2)) is applied to convert urinary measurements of biomarkers to daily intake of parent compounds.

$$EDI\left(\frac{\frac{\mu g}{kg\ bw}}{d}\right) = \frac{C_U\left(\frac{\mu mol}{L}\right) \times V_U(L) \times MW_P\left(\frac{g}{mol}\right)}{F_{UE} \times BW\,(kg)} \quad (2)$$

EDI, Estimated Daily Intake; C_U, molar concentration of DMPs or DEPs; V_U, the total urinary volume excreted within 24 h; MW_P, molecular weight of the parent compound; F_{UE}, urinary excretion factor of the parent compound, BW, the reference body weight.

Calculated EDI was expressed as malathion, diazinon, parathion-ethyl, phorate and dimethoate based on the urinary levels of their respective non-specific biomarkers. Exposure to malathion and dimethoate was calculated from the urinary levels of DMPs and exposure to parathion, diazinon and phorate from DEPs. Two highly toxic (HT) and three moderately toxic (MT) OPs were selected. Parathion is classified as HT with LD_{50} value 3–8 mg/kg and it is no longer registered for any use in USA. Phorate is also classified as HT. Diazinon, malathion and dimethoate are MT. Diazinon is a highly lipophilic compound which is stored in human body and released slowly and therefore toxicity takes place slowly (US EPA, 2013). The parameters for pesticides that were used in Equation (2) are presented in Table 1. Parameters of urine volume and body weight for children were different depending on the age (Institute of Medicine, 1998). The urine output varied from 0.45 to 1.40 L and the body weight from 10 to 60 kg. Urine volume for adults was set to 1.50 L (Dirtu et al., 2013) and body weight to 70 kg (WHO, 2006).

EDI was compared to ADI via the calculation of the HQ which is the ratio of the potential exposure to a substance (EDI) to the levels at which no adverse effects are expected (ADI) (EFSA, 2013). HQ values of two pesticides were summed (one for urinary DMPs and one for DEPs) to obtain the HI and to estimate the increased risk due to co-exposure to two compounds. Although guideline values and safe levels for human exposure to pesticides are for single compounds, we cannot circumvent the fact that humans are multiply exposed to mixtures of substances and risk assessment to single pollutants underestimates the real health effects (Castorina et al., 2003; Sexton, 2012; Tsatsakis et al., 2016, 2017). OPs are considered to have the same mechanism of action and health effects to humans, although the degree of the risk varies.

3. Results and discussion

3.1. Biomonitoring data of OPs in general population

The environmental sources of exposure are generally common for all populations due to the widespread use of pesticides in worldwide scale. However, exposure for each population differs significantly depending on lifestyle and socioeconomic factors. Urine samples collected from pregnant women and the general population from Palestine, Jerusalem and Israel were analyzed for six DAPs (Abdeen et al., 2015; Berman et al., 2013). Notably, Palestinian women had significantly lower levels of urinary DAPs ($p = 0.041$) than residents from the other regions, possibly due to lower consumption of fruits and vegetables in

Table 1
Parameters for pesticides used for the estimation of daily intake and HQ.

Pesticide	MW (g/mol)	F_{UE}	ADI (μg/kg bw/d)	Toxicity based on LD50 values (US EPA, 2013)
Malathion	330.36	0.21 (Bouchard et al., 2003)	300 (JMPR, 2016)	Moderately Toxic, MT
Diazinon	304.35	0.66 (Garfitt et al., 2002)	5 (JMPR, 2006)	Moderately Toxic, MT
Parathion	291.30	0.39 (Morgan et al., 1977)	4 (JMPR, 2000)	Highly Toxic, HT
Phorate	260.37	0.77 (JMPR, 2004)	0.70 (JMPR, 2005)	Highly Toxic, HT
Dimethoate	229.26	0.90 (Hoffmann and Papendorf, 2006; Krieger and Thongsinthusak, 1993)	2 (JMPR, 2003)	Moderately Toxic, MT

*The respective molecular weights of DMP, DMTP, DMDTP, DEP, DETP and DEDTP were used to convert urinary concentrations μg/L to molar concentrations μmol/L (g/mol: 126.05; 142.11; 157.17; 154.10; 170.17; 186.22).

the Palestinian population. Although these three regions are geographically close to each other, human exposure to pesticides had significant differences, reflecting differences in culture, diet, habits and pesticide regulation. This statement was also supported by another study conducted in Australia during 2012–2013 (Heffernan et al., 2016). Pool urine samples from 2400 individuals were combined and analyzed for specific metabolites and DAPs. DMTP and the specific metabolites TCPY and PNP were associated with age in younger and older individuals, although the correlation of DMDTP and DETP with age was weak indicating that except for age and gender, other factors like lifestyle may influence biomonitoring data. Except for DEDTP which was not detected in any sample, detection rates were over 75% (DMDTP) for all DAPs. Mean values were low, namely 13.6, 10.6, 0.4, 6.2, and 1.3 μg/L for DMP, DMTP, DMDTP, DEP, and DETP, respectively. Mean values for the specific metabolites MDA, IMPY and PNP were 1.0, 0.4, and 1.8 μg/L, respectively. TCPY was the compound with the highest levels, mean concentration 23.0 μg/L and range 2.0–36.8 μg/L (Table 2).

High urinary DAPs in pregnant women from Canada (MIREC study) were associated with the consumption of sweet peppers, tomatoes,

Table 2
Concentrations of organophosphate metabolites in urine collected from environmentally exposed population.

Reference	Country, year	N, Population	Units	Compounds	Mean ± SD	Median	Range/Max	% Detection Frequency
Harley et al., 2016	USA, 1999–2000	484, pregnant women	nmol/g	sumDMPs	76.3 ± 3.6	78.5	3228.9	100.0
				sumDEPs	16.4 ± 3.1	16.3	453.5	100.0
				sumDAPs	105.6 ± 3.0	102.0	3359.8	100.0
	USA, 2003–2006	328, pregnant women	nmol/g	sumDMPs	44.6 ± 4.3	46.4	1686.8	95.2
				sumDEPs	11.2 ± 4.5	14.5	199.1	83.1
				sumDAPs	66.8 ± 3.5	70.1	1715.4	98.4
	USA, 1998–2006	82, pregnant women	nmol/g	sumDMPs	11.4 ± 20.6	29.1	1584.2	74.4
				sumDEPs	7.4 ± 13.4	19.4	231.8	80.5
				sumDAPs	42.9 ± 7.4	59.6	1622.8	92.7
	USA, 1998–2002	341, pregnant women	nmol/g	sumDMPs	41.1 ± 7.6	47.3	8498.5	94.4
				sumDEPs	12.8 ± 9.0	19.4	1629.5	85.6
				sumDAPs	75.5 ± 5.5	47.3	8498.6	95.9
Ye et al., 2016	Canada, 2010	3466, general population, 20-79	nmol/g	DMP	27.5 ± 2.0	27.5	13.1–56.9	76.4
				DMTP	17.2 ± 1.3	14.5	< LOD-55.4	66.7
				DMDTP	NC	< LOD	< LOD-5.5	36.4
				DEP	17.5 ± 0.8	17.9	9.8–33.4	77.9
				DETP	NC	< LOD	< LOD	36.1
				DEDTP	NC	< LOD	< LOD	2.3
Sokoloff et al., 2016	Canada, 2008–2011	1884, pregnant women	nmol/L	DMP	23.0	23.0	1507.0	79.0
				DMTP	20.0	21.0	690.0	80.0
				DMDTP	2.0	2.0	518.0	51.0
				DEP	14.0	14.0	22,064.0	77.0
				DETP	3.0	3.0	294.0	53.0
				DEDTP	NC	NC	35.0	2.0
Heffernan et al., 2016	Australia, 2012–2013	2400, general population	μg/L	DMP	13.6	–	–	100.0
				DMTP	10.6	–	–	100.0
				DMDTP	0.4	–	–	75.0
				DEP	6.2	–	–	100.0
				DETP	1.3	–	–	83.0
				DEDTP	< LOD	–	–	NC
				TCPY	23.0	–	2.0–36.8	100.0
				MDA	1.0	–	–	100.0
				IMPY	0.4	–	–	91.6
				PNP	1.8	–	–	100.0
Abdeen et al., 2015	Palestine, 2010–2012	148, pregnant women, 28.2 ± 6.7	μg/L	DMP	3.7	4.9	203.3	89.7
				DMTP	8.6	8.6	1523.1	97.2
				DMDTP	0.4	0.4	314.3	69.0
				DEP	2.9	2.7	205.6	98.6
				DETP	0.9	0.8	52.1	71.7
				DEDTP	0.02	0.01	2.8	42.8
	Jerusalem, 2011	72, pregnant women, 31.2 ± 4.8	μg/L	DMP	10.3	12.1	247.8	100.0
				DMTP	12.7	9.9	452.8	100.0
				DMDTP	0.5	0.3	27.8	57.0
				DEP	2.7	16.2	49.3	94.5
				DETP	0.6	0.6	11.8	75.3
				DEDTP	0.1	0.1	2.5	60.0
Ye et al., 2015	Canada, 2007–2009	5604, general population	nmol/L	DMP	23.5	24.3	9.0–57.9	77.4
				DMTP	14.3	14.3	< LOD-49.2	67.0
				DMDTP	NC	< LOD	< LOD-4.1	36.6
				DEP	14.9	15.1	7.7–30.8	78.6
				DETP	NC	< LOD	< LOD-5.8	37.4
				DEDTP	NC	< LOD	< LOD	2.6
Melgarejo et al., 2015	Spain, 2012–2013	116, Men	μg/L	DMP	1.3 ± 4.3	1.5	–	86.8
				DMTP	1.0 ± 14.5	1.4	–	85.2
				DMDTP	0.1 ± 0.7	0.1	–	70.2
				DEP	2.6 ± 4.7	3.0	–	96.7
				DETP	0.9 ± 25.8	0.8	–	98.3
				DEDTP	0.05 ± 0.03	0.1	–	61.9

(continued on next page)

Table 2 (*continued*)

Reference	Country, year	N, Population	Units	Compounds	Mean ± SD	Median	Range/Max	% Detection Frequency
Lewis et al., 2015	USA, 2010–2012	54, pregnant women	μg/L	TCPY	0.4	0.5	3.3	86.2
				IMPY	< LOD	< LOD	1.6	14.5
				MDA	< LOD	< LOD	4.1	10.5
				PNP	0.5	0.5	11.4	90.1
				DMP	1.4	< LOD	51.2	46.0
				DMTP	0.8	1.0	73.3	62.7
				DMDTP	0.2	< LOD	5.2	38.7
				DEP	0.9	< LOD	158.0	32.7
				DETP	0.5	< LOD	17.1	51.3
				DEDTP	< LOD	< LOD	0.8	2.7
	USA, 2009–2010	355, pregnant women	μg/L	TCPY	0.8	1.0	23.8	85.1
				IMPY	< LOD	< LOD	12.5	18.1
				MDA	< LOD	< LOD	20.0	16.9
				PNP	0.5	0.5	39.8	79.7
				DMP	< LOD	< LOD	194.0	41.2
				DMTP	2.1	1.9	267.0	78.8
				DMDTP	0.5	< LOD	35.9	21.5
				DEP	0.7	< LOD	78.6	33.9
				DETP	0.7	< LOD	32.0	46.7
				DEDTP	< LOD	< LOD	1.1	0.4
Zhang et al., 2014	China, 2011–2012	249, pregnant women	μg/L	DMP	18.0	24.0	334.0	94.8
				DMTP	8.5	11.8	138.0	83.9
				DEP	7.1	5.4	167.1	95.6
				DETP	5.6	7.0	133.0	88.8
				DEDTP	NC	< LOD	6.61	6.8
Berman et al., 2013	Israel, 2011	120, general population, 40.9 ± 13.4	μg/L	DMP	13.5	13.6	116.5	99.0
				DMTP	8.0	7.1	246.3	100.0
				DMDTP	0.4	0.3	41.9	73.0
				DEP	1.9	2.0	13.5	98.0
				DETP	0.6	0.6	5.4	76.0
				DEDTP	NC	NC	1.8	44.0
Davis et al., 2013	USA, 2012	55, general population	μg/L	IMPY	0.8	–	0.2–2.0	25.5
				MDA	1.2	–	0.4–5.9	29.1
				PNP	1.4	–	0.04–8.2	92.7
				TCPY	1.9	–	0.1–6.1	96.4
Wang et al., 2012	China, 2006–2007	187, pregnant women	μg/L	DMP	17.2	–	269.2	83.4
				DMTP	8.01	–	109.7	89.3
				DEP	6.0	–	109.7	95.7
				DETP	6.3	–	131.8	93.6
				DEDTP	NC	–	5.1	5.3
Ye et al., 2008	Netherlands, 2002–2006	100, pregnant women	nmol/L	DMP	79.9	85.7	< LOD-765.0	99.0
				DMTP	60.9	74.6	0.7–774.0	100.0
				DMDTP	2.3	2.5	< LOD-25.8	96.0
				DEP	13.0	13.0	< LOD-253.0	99.0
				DETP	4.7	4.7	< LOD-218.0	96.0
				DEDTP	0.2	0.2	< LOD-26.8	81.0
				TCPY	6.3	5.9	0.8–797.0	100.0
Curwin et al., 2007	USA, 2001	98 family members	μg/L	TCPY	–	–	1.8–54.0	100.0
Aprea et al., 2004	Italy, 2001	124, general population	nmol/g	sumDMPs	210.3 ± 199.3	145.7	30.6–696.7	–
Koch et al., 2001	Germany	50, general population	μg/L	TCPY	4.8	1.4	0.12–124.8	100.0
				DMP	43.1	30.8	–	–
				DMTP	45.7	22.7	–	–
				DEP	6.6	4.2	–	–
				DETP	3.7	3.8	–	–

*NC, not calculated.

beans and dry peas, citrus fruits, apple juice, white wine, green and herbal tea, soy and rice beverages and whole grain bread (Sokoloff et al., 2016). The main variables associated with higher exposure to OPs were higher education, fasting and following a diet full of fruits and vegetables.

3.2. Biomonitoring data of OPs in occupationally exposed adults

MMA, a specific metabolite of malathion, was measured in urine samples from sprayers after malathion application (Table 3). Excretion of malathion via urine was very rapid reaching its maximum level in about 6 h after application (Tuomainen et al., 2002). Dermal exposure to malathion occurred through upper and lower limbs, 19% and 48% respectively, hands and chest accounted for 30% of dermal exposure while back and head only 3%. It has been shown that the use of personal protective measures and personal hygiene has a significant positive impact in reducing exposure of agricultural workers to OPs. Wearing gloves and full body coveralls while handling and applying pesticides have been positively associated with lower body burden of OPs ($p < 0.05$) and immediate change of uniform after application of pesticides has been associated with lower urinary DAPs (Koureas et al., 2014).

Margariti and Tsatsakis (2009) were the first to report measurement of DAPs in head hair from occupationally exposed population. Approximately, the 70%, 40% and 20% of the samples were positive for DEP, DMP and DMTP respectively whereas the detected levels ranged from 100 to 460 pg/mg for all analytes. In hair samples from population in Sri Lanka DEP, DETP, DEDTP and DMP were detected at 83.3 pg/mg,

Table 3
Concentrations of organophosphate metabolites in urine collected from occupationally exposed population.

Reference	Country, year	N, Population, years old	Units	Compounds	Mean ± SD	Median	Range	% Detection Frequency
Shomar et al., 2014	Qatar, 2012–2013	125, farmers, 21-35	nmol/L	DMP	44.6	–	185.0	93.0
				DMTP	31.8	–	164.0	89.0
				DMDTP	1.2	–	42.3	67.0
				DEP	9.8	–	114.0	92.0
				DETP	14.2	–	86.3	87.0
				DEDTP	0.4	–	2.4	62.0
Koureas et al., 2014	Greece, 2010	77, farmers	μg/g	DMP	–	6.9	2.6–15.4	97.4
				DEP	–	10.9	5.6–24.8	98.7
				DETP	–	7.6	2.3–23.5	100.0
				DEDTP	–	0.9	0.6–1.6	100.0
Kongtip et al., 2014	Thailand, 2011–2012	56, exposed pregnant women	nmol/L	DMP	–	37.7	121.5	77.9
				DEP	–	14.6	72.0	67.4
				DETP	–	< LOD	464.4	47.7
				DEDTP	–	< LOD	476.8	44.2
Kokkinaki et al., 2014	Greece, 2013	31, farmers, 53.6 ± 15.1	μg/L	DMP	9.0 ± 5.8	8.6	–	100.0
				DEP	74.2 ± 53.8	56.5	–	100.0
				DETP	944.7 ± 746.4	731.6	–	100.0
				DEDTP	0.3 ± 0.2	0.2	–	90.0
Phung et al., 2012	Vietnam, 2009	108, farmers	μg/g	TCPY	47.5 ± 12.8	–	3.0–678.0	
Dalvie et al., 2011	South Africa	20, farmers	μg/L	DMP	–	< LOD	< LOD-98.3	–
				DMTP	–	602.1	< LOD-4118	–
				DMDTP	–	17.4	< LOD-227.5	–
				DETP	–	< LOD	< LOD-22.1	–
Arcury et al., 2009	USA, 2007	287, farmers	μg/L	DMP	–	1.0	359.09	41.3
				DMTP	–	3.6	2577.8	78.3
				DMDTP	–	0.04	577.6	33.3
				DEP	–	0.9	127.4	40.5
				DETP	–	0.2	142.0	32.3
				DEDTP	–	< LOD	96.3	8.1
Curwin et al., 2007	USA, 2001	113, exposed family members	μg/L	TCPY	–	–	5.6–87.0	100.0
Aprea et al., 2004	Italy, 2001	18, farmers, 34-36	nmol/g	sumDMPs	310.6	404.2	79.8–1213.0	–

34.7 pg/mg, 34.5 pg/mg and 3.0 pg/mg, respectively, and their respective detection rates were 82%, 90%, 82% and 42% (Knipe et al., 2016). Biomonitoring data from population groups with occupational exposure to OPs (farmers and sprayers) showed increased levels of DAPs in both hair and urine samples (Kokkinaki et al., 2014; Koureas et al., 2014). Both matrices gave higher levels and detection rates of DAPs in agricultural workers than in rural residents-control group and this differentiation was statistically significant ($p < 0.001$). These studies indicated that hair analysis can provide comparable results to urine analysis and the differentiation between occupational exposed population and general population is proportionate in both matrices. This conclusion also came up from animal studies conducted in rats (Hardy et al., 2015) and rabbits (Kavvalakis et al., 2013) orally exposed to pesticides. Concentrations from urine and hair samples were comparable and the suitability of hair analysis for the detection of the parent compounds and their respective metabolites was confirmed.

3.3. Biomonitoring data of OPs in children

Children could be included in the general population group since only environmental or dietary exposure to pesticides can occur. However, they are a sensitive population group due to their low body mass and the increased health risk because their organism is still under development. DAPs were measured in urine extracted from disposable diapers from 116 children in Japan during June–July 2015 (Oya et al., 2016). The mean concentrations ranged from 0.6 μg/L (DETP) to 6.0 μg/L (DEP), maximum levels were detected for DMTP, DMP and DEP, 130.3 μg/L, 100.8 μg/L and 83.6 μg/L respectively (Table 4). The detection rate ranged from 49.1% (DEDTP) to 100% (DMTP and DETP). The large variability of urinary pesticide metabolite concentrations often observed in children has been attributed to the episodic rather than systematic exposure or variability in children's metabolic rates (Kissel et al., 2005; Lambert et al., 2005) and it demands the analysis of multiple urine samples from each individual for the accurate assessment of pesticide exposure.

Take-home pesticide exposure is also a significant source in houses of farmworkers (Curwin et al., 2007). Pesticides were detected in urine from 117 children living in farm and non-farm households. The comparison between the two groups showed statistically significant differences ($p < 0.0001$) and higher exposures for farm children especially if their father had recently applied pesticides in the fields. Urinary levels between family members were correlated indicating common source of exposure. A study conducted in USA during 2002, compared the occurrence of OPs in indoor environmental matrices such as dust, air, floor and toys, in farmworkers' houses with the DAPs detected in spot and overnight urine samples from their children (Bradman et al., 2007). Although, the pollutants were detected in all environmental and biological matrices, the correlations between them were not significant. DEPs in urine were positively correlated with diazinon in dust, socks and union suit ($p < 0.05$) but non-significantly with diazinon levels in toys, whereas levels of chlorpyrifos in toys were positively correlated with urinary DEPs ($p < 0.05$). The use of personal protective measures and hygiene behavior from agricultural workers has a significant positive impact in reducing the take-home pesticide exposure pathway (Koureas et al., 2014). Wearing gloves and uniform during pesticide application and immediate cloth removal before entering home can significantly reduce the body burden of the family members ($p < 0.05$).

Similarly to biomonitoring data for adults, children who live in agricultural regions have higher urinary levels of pesticides compared to those living in urban communities (Lambert et al., 2005). DMTP was the most commonly detected metabolite in urine from children living in areas where pears, cherries and berries were cultivated. Median urinary levels for children in rural areas were 17.5 μg/L, 19.0 μg/L and 41.0 μg/L whereas urinary DMTP in children from urban area was 6.5 μg/L. The large variability in urinary DAP levels across the work season was attributed to the different types and amounts of the applied pesticides and the frequency of application. In a similar study conducted in Spain

Table 4
Concentrations of organophosphate metabolites in urine collected from children.

Reference	Country, year	N, age	Units	Compounds	Mean ± SD	Median	Range/Max	% Detection Frequency
Osaka et al., 2016	Japan, 2012–2013	703, 3 years old	μg/L	DMP	14.0	14.3	92.4	100.0
				DMTP	5.2	5.5	230.4	95.5
				DEP	5.3	5.3	67.6	99.1
				DETP	0.6	0.6	22.5	89.7
Oya et al., 2016	Japan, 2015	116, 18.8 ± 0.7 months	μg/L	DMP	3.6	3.4	100.8	94.0
				DMTP	3.9	4.0	130.3	100.0
				DMDTP	0.9	1.0	6.2	99.1
				DEP	6.0	6.7	83.6	84.5
				DETP	0.6	0.6	55.9	100.0
				DEDTP	NC	< LOD	1.4	49.1
Ye et al., 2016	Canada, 2010	980, 12-19	nmol/g	DMP	27.1 ± 2.1	29.0 ± 2.7	–	82.3
				DMTP	14.0 ± 1.3	14.1 ± 1.5	–	68.6
				DMDTP	NC	< LOD	–	35.4
				DEP	16.8 ± 1.3	16.9 ± 1.3	–	82.0
				DETP	NC	< LOD	–	44.6
				DEDTP	NC	< LOD	–	4.4
Myridakis et al., 2016	Greece, 2007–2008	500, 4.2 ± 0.2	μg/L	DMP	NC	< LOD	< LOD-8.9	24.6
				DMTP	3.8	4.0	< LOD-410.3	98.2
				DMDTP	0.1	< LOD	< LOD-61.4	49.4
				DEP	1.9	2.0	< LOD-93.1	93.6
				DETP	0.9	1.1	< LOD-30.5	93.0
				DEDTP	NC	< LOD	< LOD-5.8	21.0
Ueyama et al., 2014	Japan, 2012–2013	225, 3 years old	μg/L	DMP	14.4	–	–	100.0
				DMTP	5.3	–	–	98.0
				DEP	5.5	–	–	99.0
				DETP	0.6	–	–	80.0
Roca et al., 2014	Spain, 2010	125, 6–11 years old	μg/g	DMP	8.6 ± 43.2	< LOQ	416.8	18.0
				DMTP	5.4 ± 18.1	< LOQ	139.1	39.0
				DMDTP	1.0 ± 3.4	< LOQ	28.7	9.0
				DEP	4.0 ± 7.7	2.3	58.0	79.0
				DETP	1.7 ± 4.3	< LOQ	36.2	36.0
				DEDTP	NC	< LOQ	< LOQ	NC
				TCPY	5.7 ± 12.5	3.4	123.9	86.0
				IMPY	9.8 ± 16.8	5.2	150.0	57.0
				PNP	1.4 ± 1.7	0.9	14.0	53.0
				DEAMPY	2.8 ± 10.4	< LOQ	100.3	48.0
Guodong et al., 2012	China, 2008	301, 23–25 months	μg/L	DMP	2.5	< LOD	< LOD-186.9	41.9
				DMTP	1.6	< LOD	< LOD-80.8	36.5
				DEP	1.8	1.2	< LOD-32.2	71.8
				DETP	3.2	2.9	< LOD-55.4	69.1
				DEDTP	NC	< LOD	< LOD-3.8	2.7
Ding et al., 2012	China, 2008	268, 2 years old	nmol/L	sumDMPs	34.0	18.3	–	35.4–40.7
				sumDEPs	40.7	36.9	–	2.6–71.6
				sumDAPs	87.0	75.7	–	–
Naeher et al., 2010	USA, 2001	203, 4–6 years old	μg/L	DMP	9.6	5.1	80.6	75.0
				DMTP	17.4	3.8	270	88.4
				DMDTP	2.8	0.6	57.7	77.9
				DEP	6.0	4.1	79.7	92.0
				DETP	1.6	0.6	17.3	97.5
				DEDTP	0.2	< 0.1	1.8	49.0
Panuwet et al., 2009	China	207, 12–13 years old	μg/L	PNP	2.7	2.9	0.3–19.5	98.0
				TCPY	2.4	2.6	0.2–34.5	92.0
				IMPY	NC	NC	< LOD-11.8	< 1.0
				MDA	0.3	0.3	0.3–2.1	25.0
				DEAMPY	0.2	0.1	0.3–6.3	5.0
Lu et al., 2008	USA, 2003–2004	23, 3–11 years old	μg/L	MDA	4.6	1.6	< LOD-263.0	66.0
				TCPY	5.1	3.7	< LOD-32.0	91.0
				IMPY	0.2	NC	< LOD-15.0	9.0
				DEAMPY	0.3	NC	< LOD-18.0	25.0
Arcury et al., 2007a	USA, 2004	60, 1–6 years old	μg/L	TCPY	1.9	2.5	–	83.3
				IMPY	0.6	0.5	–	55.0
				MDA	NC	0.2	–	28.3
				PNP	1.0	1.6	–	90.0
Arcury et al., 2007b	USA, 2004	60, 1–6 years old	μg/L	DMP	5.1	2.8	< LOD-24.9	6.7
				DMTP	21.2	6.7	< LOD-183.3	20.3
				DMDTP	2.7	0.7	< LOD-27.1	21.7
				DEP	8.6	6.0	< LOD-68.7	18.6
				DETP	1.4	0.8	< LOD-12.4	15.0
				DEDTP	0.06	< LOD	< LOD-0.6	83.3
Bradman et al., 2007	USA, 2002	20, 5–27 months	nmol/L	sumDEPs	11.0	13.0	1.3–310.0	2.6–43.6
				sumDMPs	66.0	85.0	4.1–1100.0	33.3–82.1
				sumDAPs	99.0	100.0	5.4–1300.0	100.0

(*continued on next page*)

Table 4 (*continued*)

Reference	Country, year	N, age	Units	Compounds	Mean ± SD	Median	Range/Max	% Detection Frequency
Valcke et al., 2006	Canada, 2003	89, 3–7 years old	μg/g	DMP	20.0	22.9	0.7–380.0	98.2
				DMTP	18.8	21.9	0.4–1381.0	91.6
				DMDTP	2.8	2.9	0.3–227.0	67.6
				DEP	4.8	5.8	0.4–183.0	86.7
				DETP	0.7	0.4	0.4–175.0	27.6
				DEDTP	0.4	0.4	0.2–1.9	0.6
Kissel et al., 2005	USA, 1998	13, 2.5–5.5 years old	nmol/L	DMTP	250.0	110.0	2200.0	97.0
				DETP	18.0	11.0	240.0	67.0
				MDA	20.0	5.5	400.0	71.0
				PNP	32.0	16.0	270.0	96.0
				TCPY	46.0	46.0	130.0	79.0
Heudorf et al., 2004	Germany, 1998	649, < 18 years old	μg/L	DMP	37.8 ± 66.0	16.7	750.6	NC
				DMTP	44.7 ± 109.9	16.8	1668.5	NC
				DMDTP	3.0 ± 14.6	< LOD	288.8	NC
				DEP	5.2 ± 8.4	3.0	98.0	NC
				DETP	2.3 ± 7.4	< LOD	82.8	NC
				DEDTP	0.01 ± 0.1	< LOD	0.5	NC

*NC, not calculated.

(Roca et al., 2014), a total of 15 metabolites (OPs, pyrethroid insecticides, herbicides) were detected in the urine samples from school children. The detection frequencies of DAPs ranged from 18% to 39% and the most frequently detected metabolites were TCPY (86%), DEP (79%), IMPY (57%) and PNP (53%). Mean concentrations were between 0.5 and 3.4 μg/g creatinine and the highest levels were for TCPY and IMPY, 3.4 μg/g creatinine and 3.3 μg/g creatinine, respectively. DEP was higher in children from agricultural area whereas IMPY metabolite was higher in urban children. Age, vegetable consumption and residential use of pesticides were associated with detectable urinary levels of TCPY, IMPY and DEP. Morgan and Jones (2013) associated dietary habits of preschool children and urinary biomarkers of exposure to chlorpyrifos. The frequency of consumption of fresh apples ($p = 0.04$), fruit juices ($p = 0.02$), butter, chicken and turkey meats ($p < 0.05$) were significantly associated with high exposure to chlorpyrifos, similarly to the results from the MIREC study, previously mentioned, in adults (Sokoloff et al., 2016).

3.4. Associations with health effects

The real health effects and mechanisms of action of OPs in humans remain unclear and data from studies in literature vary. Oulhote and Bouchard (2013) reported no associations between OP exposure and behavioral scores in children, although other studies correlate urinary DAPs from children with increased odds of behavioral problems (Bouchard et al., 2011) namely Attention Deficit Hyperactivity Disorder (ADHD), poor mental development (poor IQ scores), pervasive developmental problems (Eskenazi et al., 2007) and oxidative DNA damage (Ding et al., 2012). Prenatal or early life exposure to OPs has been linked with adverse effects on neurodevelopment in early infancy (Eskenazi et al., 2007), poor intellectual development in 7-year old children (Gunier et al., 2016; Bouchard et al., 2011), respiratory outcomes (Raanan et al., 2015), hypospadias in offspring (Michalakis et al., 2014) and a study conducted in China noted that prenatal exposure to OPs was one of the most important factors affecting Neonatal Behavioral Neurological Assessment (NBNA) scores (Zhang et al., 2014). In a meta-analysis study, childhood leukemia was associated with maternal occupational exposure during gestation (Wigle et al., 2009) and this association was stronger for groups with high exposure levels. Another study in China associated an increased risk of the disease with the household use of mosquito repellent (Zhang et al., 2015).

Additionally, in utero exposure to OPs has been linked with shortened gestation, reduced birth weight (Naksen et al., 2015; Rauch et al., 2012) and increase in maternal cortisol which poses risk for newborn health later in life (Cecchi et al., 2012). Wang et al. (2012) found associations with duration of gestation but no effects on fetal growth. Similarly, Harley et al. (2016) found no significant associations between exposure to OPs and birth weight, length or head circumference, whereas Koutroulakis et al. (2014) found positive correlations between birth length and DMPs in amniotic fluid. Shapiro et al. (2016) noted no associations between maternal exposure to OPs during pregnancy and Impaired Glucose Tolerance (IGT) and Gestational Diabetes Mellitus (GDM) and Yolton et al. (2013) mention minimal or no impact on neurobehavior of young infants. There are no observed associations with gastrointestinal effects on young children at the age of 1–4 years old (Jones et al., 2014). In contrast with previous studies, Guodong et al. (2012) found no associations between OP metabolites in urine from children and neurodevelopment. According to some views, the appeared outcomes differ by race/ethnicity and PON1 genotypes (Naksen et al., 2015; Rauch et al., 2012; Harley et al., 2011; Tsatsakis et al., 2009, 2011) which together with enzyme activity levels suggest whether the infant is susceptible to the effects of OP exposure.

Exposure of adults to OPs has been linked with reduced sperm concentration (Perry et al., 2007), decreased sperm counts and motility, as well as altered reproductive hormone in male (Melgarejo et al., 2015). Urinary levels of DAPs have been inversely associated with inhibin B, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) serum levels and testosterone (Blanco-Muñoz et al., 2010). Authors hesitate to characterize OPs as endocrine disruptors since the resulted associations are weak and most hormonal values fall within the normal range. The impact of OP metabolites on obesity and cardiometric health remains unclear (Ranjbar et al., 2015) since OP metabolites affect in a different way depending on the body mass index of the individual. Moreover, although OPs metabolites seem to have adversely effects on HDL and LDL, DMTP was linked with high HDL, low LDL and low total cholesterol resulting in a more favorable lipid outcome. Authors note the need for further research. Alzheimer's disease is a form of dementia and its association with exposure to pesticides is a point of interest for several studies (Zaganas et al., 2013) but data are limited and contradictory. OPs have a possible role in the pathogenesis of Altzheimer's disease because AChe is also a legitimate therapeutic target in the disease. As already mentioned, not all individuals who have been exposed to pesticides suffer from dementia and other neurologic diseases due to their genetic composition and detoxification genes which protect the organism from xenobiotics (Tsatsakis et al., 2011).

Motsoeneng and Dalvie (2015) showed no associations between occupational exposure to OPs and neurotoxic effects in adults but this can be attributed to study limitations. Rothlein et al. (2006) linked poor performance of agricultural workers on neurobehavioral tests with

occupational exposure to OPs and Rastogi et al. (2009) indicated increased oxidative stress in pesticide sprayers, enhanced lipid peroxidation, cholinesterase inhibition and cell damage. Revision of several studies on neurobehavioral effects of occupationally exposed group to OPs show contradictory results (Colosio et al., 2003). There are studies that report increased levels of anxiety, reduced concentration and increased hand vibration threshold for long term occupationally exposed groups although other studies observed no difference in neurological or behavioral parameters between pesticide sprayers and controls. When acute OP poisoning occurs, the neurobehavioral impairment is greater in individuals with severe poisoning, while in the other cases there is a reduction in AChe activity without other neurotoxic effects. Data sufficiently indicate that in the occupationally exposed group, neurobehavioral impairment is a possible consequence of both acute poisoning and long-term exposures (Colosio et al., 2009).

3.5. Estimated exposures to OPs

Results of the EDI calculation are presented in Table 5. EDI of malathion is higher than the other pesticides for all population groups due to its low Fue (0.21). However, ADI for malathion is higher than the other OPs resulting in an HQ value far below unit, meaning very low risk for health (Fig. 1, Table 6). The pattern of EDIs is the same for all population groups: malathion > dimethoate > parathion > diazinon > phorate while for HQ it changes to dimethoate > phorate > parathion > diazinon > malathion. For parathion and phorate which are HT the median HQs for children are far below unit, 0.239 and 0.618 respectively, while for farmers 0.363 and 0.979 respectively.

Pregnant women seem to be less exposed to OPs than other population groups and a possible explanation could be the increase of their body mass (medians EDI: 0.11–1.52 μg/kg bw/day). Calculated daily intakes are considered to be safe since maximum HQ values range from 0.023 to 0.823 (Table 6). On the other hand, children have greater exposure to organophosphates compared to adults with environmental exposure to pesticides (medians EDI: 0.43–4.86 μg/kg bw/day). In general, children are highly burdened with environmental pollutants relatively to adults (general population and pregnant women), as has also been described elsewhere (Dewalque et al., 2014; Katsikantami et al., 2016; Zentai et al., 2016). Estimated exposures for children are mostly within safe levels, except for the studies in USA 1998 (Kissel et al., 2005) and 2001 (Naeher et al., 2010), Germany 1998 (Heudorf et al., 2004) and Japan 2015 (Oya et al., 2016) that HQs surpassed unit (Fig. 2).

Table 5
Descriptive statistics for Estimated Daily Intakes (EDI) of malathion, diazinon, parathion, phorate and dimethoate in general population, pregnant women, children and farmers (μg/kg bw/day).

Pesticide	min	25th	50th	75th	Max
General population					
Malathion	0.60	1.21	2.55	5.15	22.37
Diazinon	0.14	0.15	0.16	0.22	0.64
Parathion	0.22	0.24	0.25	0.36	1.03
Phorate	0.10	0.11	0.12	0.16	0.47
Dimethoate	0.10	0.20	0.41	0.83	3.62
Pregnant women					
Malathion	0.30	1.09	1.52	4.82	6.85
Diazinon	0.06	0.09	0.14	0.21	0.79
Parathion	0.09	0.14	0.23	0.34	1.27
Phorate	0.04	0.06	0.11	0.16	0.58
Dimethoate	0.05	0.18	0.25	0.78	1.11
Children					
Malathion	0.40	2.26	4.86	11.00	29.31
Diazinon	0.05	0.25	0.59	0.81	0.98
Parathion	0.08	0.41	0.96	1.31	1.59
Phorate	0.04	0.19	0.43	0.59	0.72
Dimethoate	0.07	0.37	0.79	1.78	4.75
Farmers					
Malathion	1.45	2.41	2.61	83.07	146.56
Diazinon	0.24	0.57	0.90	30.26	59.62
Parathion	0.38	0.92	1.45	49.01	96.56
Phorate	0.18	0.43	0.69	22.21	43.73
Dimethoate	0.24	0.39	0.42	13.45	23.73

Measurements from environmentally exposed adults are within safe levels except for one study in Germany (Koch et al., 2001) for which HQ for dimethoate was 1.811. Occupational exposure of farmers to OPs results in increased daily intake of pesticides with median exposures to the five organophosphates varying from 1.08 to 19.72 μg/kg bw/day and the range of the maximum values is 23.73–146.56 μg/kg bw/day (Table 5). These exposure levels are considered to be safe based on median HQs for malathion, diazinon and parathion. Median HQs for phorate and dimethoate were above unit (Table 6).

Data for children and adults were organized based on the year of sampling (Fig. 3). Urinary measurements in children and adults after 2002 tend to be constant and lower compared to previous years. Mean of DMPs and DEPs for children are 0.059 and 0.024 μmol/L, respectively and for adults 0.072 μmol/L (DMPs) and 0.026 μmol/L (DEPs). DMPs are mostly higher than DEPs indicating either greater exposure to pesticides that are metabolized to DMPs, like malathion and dimethoate, or exposure to lipophilic compounds, like diazinon, which are metabolized to DEPs and are stored in human body and slowly released. It has been described elsewhere (Clune et al., 2012) that the application of Food Quality Protection Act in 1996 for OPs in foodstuff has resulted in reduced concentrations of DAPs in urine based on biomonitoring data from National Health and Nutrition Examination Survey, NHANES during 1999–2004. The decrease for the median concentrations of DAPs was 84% (range, 63.1%–98.5%) and more specifically, 92.1% for DEPs and 73.9% for DMPs. In the present study, a trend to safer exposures to OPs has been detected for children from USA during 1998–2002 (Fig. 2), although exposure of adults to OPs seems to remain constant during 1998–2010. Data from FAOSTAT (www.fao.org/faostat/en/#home) demonstrate clearly that the use of pesticides in USA during 1990–2012 remains constant (400,975-407,779 tons of active ingredients). Use of pesticides in Germany has increased from 31,289 tons (1990) to 48,593 (2015), in Spain there is an increase by 20,000 tons whereas for China almost 1,000,000 tons. On the other hand, pesticide use in Japan during 2000–2014 has decreased by approximately 26,000 tons.

3.6. Cumulative risk assessment

In real life, human is exposed to mixture of different groups of pesticides as well as environmental pollutants which could have synergistic and additive effects (Sexton, 2012; Tsatsakis et al., 2016, 2017). Since risk assessment usually focuses on individual compounds, the current regulatory approach does not assess the overall risk of chemicals present in a mixture. The EU has recognized the need for more research on exposures to combinations of toxicants eliciting common outcomes on the same target organ or system (EFSA, 2013).

Both DMPs and DEPs have been detected in human urine in several studies (Tables 2–4) indicating exposure to mixture of OPs. Risk assessment should be carried out for possible cumulative exposure scenarios of general population, pregnant women, children and farmers. Five OPs were examined in this study, two of which are metabolized to DMPs (malathion, dimethoate) and the rest three (diazinon, phorate, parathion) are metabolized to DEPs. Thus, six exposure scenarios to OPs were assumed for each population group, combining exposure to one OP that is metabolized to DMPs and one OP that is metabolized to DEPs. HI values were calculated as the sum of HQ values of each single exposure scenario (Table 7). In the first scenario that exposure to malathion was summed with exposure to diazinon (M-DZ), exposure of all population groups were within safe levels except for some studies to farmers which were above unit. Median HI for general population,

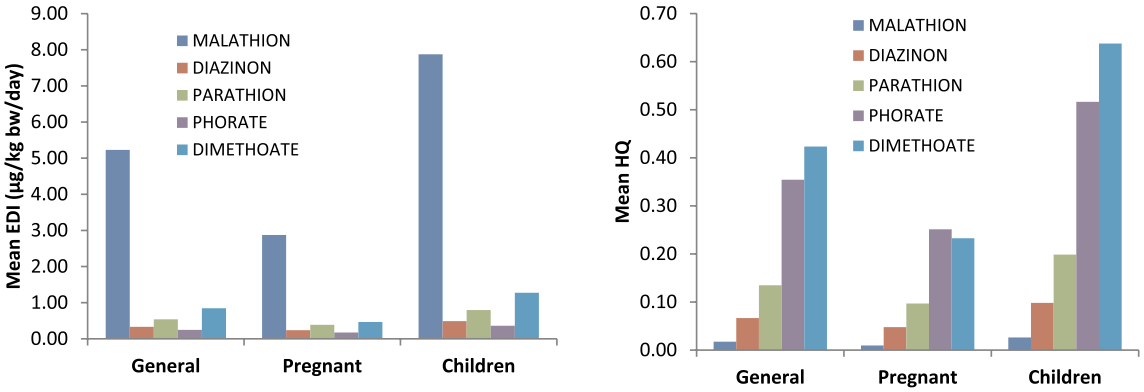

Fig. 1. Comparison of EDI (left) and HQ (right) values among different population groups.

Table 6
Descriptive statistics for Hazard Quotient (HQ) values of malathion, diazinon, parathion, phorate and dimethoate in general population, pregnant women, children and farmers.

Pesticide	Min	25th	50th	75th	max
General population					
Malathion	0.002	0.004	0.008	0.017	0.075
Diazinon	0.027	0.030	0.031	0.044	0.128
Parathion	0.055	0.060	0.063	0.090	0.258
Phorate	0.143	0.155	0.166	0.235	0.668
Dimethoate	0.049	0.098	0.206	0.417	1.811
Pregnant women					
Malathion	0.001	0.004	0.005	0.016	0.023
Diazinon	0.011	0.017	0.029	0.042	0.157
Parathion	0.023	0.035	0.058	0.084	0.318
Phorate	0.060	0.091	0.151	0.223	0.823
Dimethoate	0.024	0.088	0.123	0.391	0.554
Children					
Malathion	0.001	0.008	0.016	0.037	0.098
Diazinon	0.010	0.051	0.118	0.161	0.196
Parathion	0.020	0.103	0.239	0.326	0.396
Phorate	0.050	0.266	0.618	0.844	1.026
Dimethoate	0.033	0.183	0.393	0.891	2.373
Farmers					
Malathion	0.005	0.008	0.009	0.277	0.489
Diazinon	0.047	0.113	0.179	6.051	11.923
Parathion	0.096	0.230	0.363	12.252	24.141
Phorate	0.253	0.616	0.979	31.723	62.467
Dimethoate	0.118	0.195	0.212	6.725	11.866

pregnant women, children and farmers were 0.040, 0.033, 0.125 and 0.184 respectively. The same trend was observed for the summed exposures to malathion and parathion (M-PA). HI in the third scenario (malathion-phorate, M-PH) was higher compared to the first and second, namely for children and for farmers medians were 0.625 and 0.984 respectively and notably 8% of the studies in children were above unit, indicating increased health risk. The last three scenarios showed high HI not only for farmers, but also for general population and children. Maximum exposures of the general population, pregnant women, children and farmers to dimethoate and diazinon (D-DZ) were up to 1.939, 0.711, 2.501 and 12.118 respectively. Exposure to dimethoate and parathion (D-PA) did not differ significantly from the D-DZ scenario, except for farmers for whom risk was increased and maximum HI was up to 24.336. Cumulative exposure to dimethoate and phorate (D-PH) seem to be the worst scenario. Maximum values for all population groups are over unit (general population: 2.479; pregnant women: 1.377; children: 3.045; farmers: 62.662) and medians for children and farmers are 1.014 and 1.097 respectively.

The increase in hazard when co-exposure occurs is obvious when comparing median HQ (single exposure) and HI (two-compounds exposure) values (Tables 6 and 7). Median HQ values for children ranged between 0.016 and 0.618, for pregnant women 0.005–0.151, for general population 0.008–0.206 and for farmers 0.009–0.979. Median HI values for children ranged between 0.125 and 1.014, for pregnant women 0.033–0.298, for general population 0.040–0.296 and for farmers 0.184–1.097. The approach followed in this study based on six scenarios of co-exposure indicated that the type of parent compound or compounds that human is exposed to poses different risk for human health. Modeling aggregate and cumulative exposure is a difficult task due to the large number of compounds as well as different sources and routes of exposure.

It is not enough for risk assessment when biomonitoring studies present only concentrations of DMPs and DEPs in biological matrices. Biomonitoring data are useful when comparing exposures between different population groups or within country variations but no information can be obtained for the health risk posed from the exposure. Additional information on exposure (i.e questionnaires) is needed to trace back to the parent compounds of exposure for the estimation of daily intake and calculate the hazard value. As described elsewhere (Hernández and Tsatsakis, 2017), risk assessment considers the overall health impact of various pesticide combinations to which population may be exposed to. According to the authors, if the hypothesis of an increased hazard from cumulative exposure to chemicals were shown to be true, this would encourage public authorities and the scientific community to shift from the single-compound risk assessment to the era of cumulative risk assessment.

3.7. Study limitations

The use of the same F_{UE} parameter for children and adults for the calculation of EDI is a limitation to the obtained results since metabolism and excretion of chemical pollutants in children is different than adults. To the best of our knowledge, there are no available data of distribution and excretion of OPs in children. Furthermore, conclusions concerning comparison among studies conducted all over the world cannot be prevalent because different analytical protocols and instrumentation have been employed for the measurement of the biomarkers.

Koch et al. (2001) noticed that urine levels of metabolites were higher compared to the ingested amounts of pesticides which is expected for general population since dietary intake may be the major route of exposure, however, other sources can also become significant. On the other hand, there are indications that DAPs may already exist in the environment and their presence in an individual's biological fluids may reflect exposure to the metabolite itself. More specifically, DAPs can be formed by the hydrolytic cleavage of the parent compound on the plant after pesticide application (Koch et al., 2001; Lu et al., 2005).

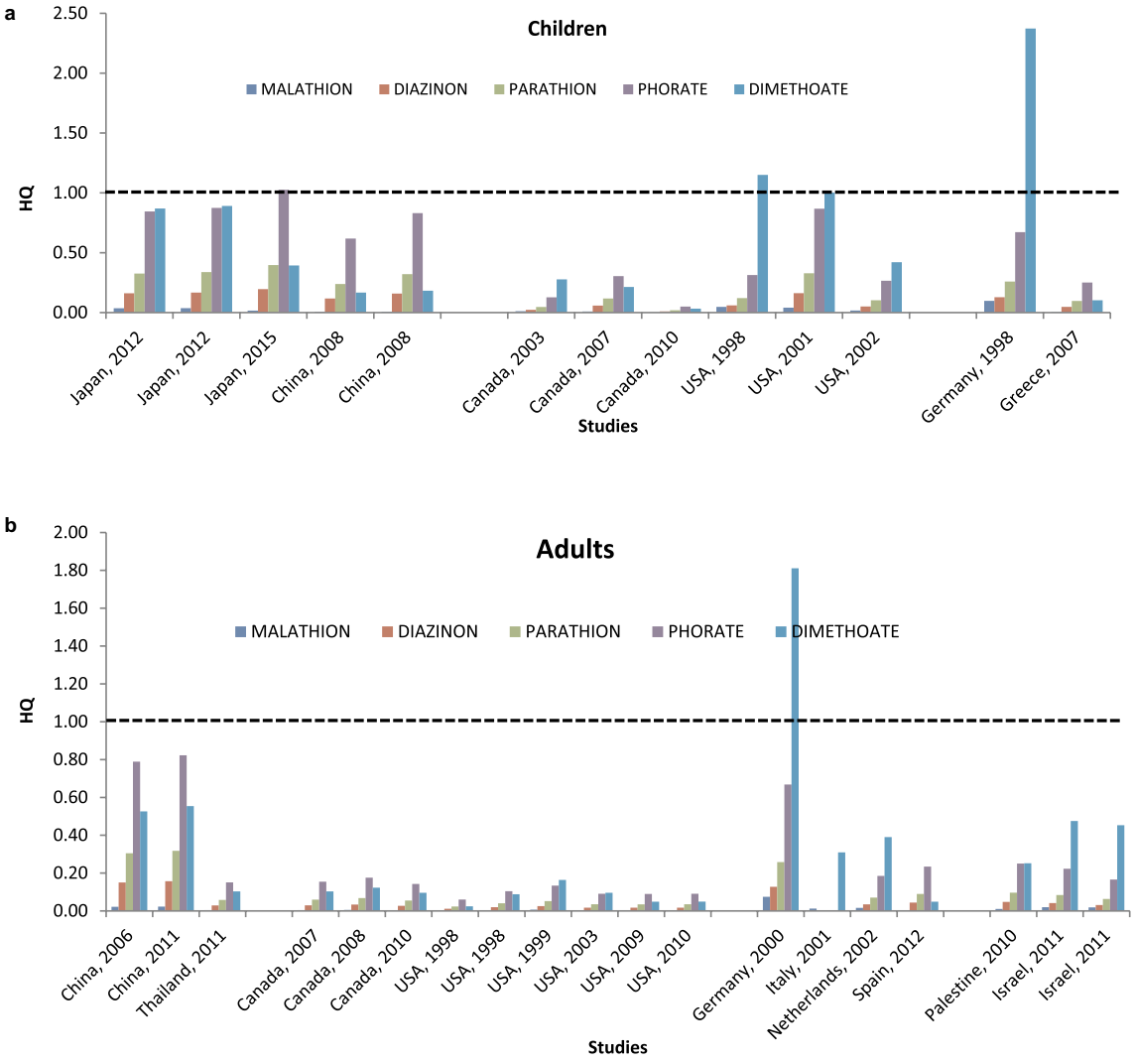

Fig. 2. HQ values of each pesticide for studies conducted in children (top) and adults (bottom). The dot line represents the border over which there is an increased potential for adverse health effects.

DAPs are not considered to pose risk for human health as their parent compounds, thus biomonitoring studies based on the non-specific metabolites of OPs have limitations.

4. Conclusions

Urinary concentrations of DAPs as presented in studies conducted all over the world indicate that human exposure to OPs shows significant differences depending on age, gender, diet and lifestyle, education level and pesticide regulation. The general trend is that rural residents are highly exposed compared to residents in urban areas. Children's exposure is attributed to episodic rather than systematic exposure, although systematic exposure can occur in houses of farmworkers due to take-home pesticide exposure. The use of personal protective measures has a significant positive impact in reducing exposure of agricultural workers as well as their family members to

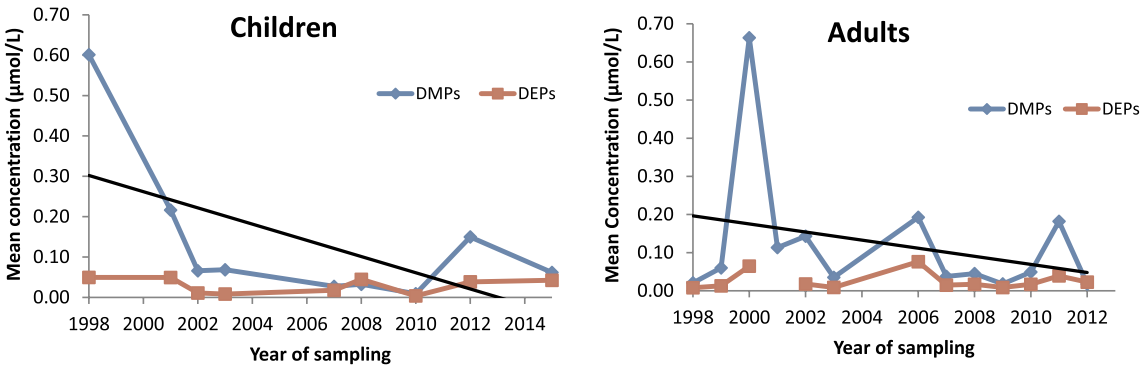

Fig. 3. Annual distribution of urinary concentrations (μnol/L) of DMPs and DEPs measured in children (left) and adults (right) during 1998–2015.

Table 7
Descriptive statistics for Hazard Index (HI) values of malathion, diazinon, parathion, phorate and dimethoate in general population, pregnant women, children and farmers. Risk assessment for six scenarios for cumulative exposure to OPs.

Scenario	min	25th	50th	75th	Max
General population					
M-DZ	0.013	0.032	0.040	0.049	0.202
M-PA	0.013	0.060	0.073	0.089	0.333
M-PH	0.013	0.150	0.172	0.224	0.743
D-DZ	0.093	0.126	0.221	0.441	1.939
D-PA	0.138	0.154	0.236	0.465	2.069
D-PH	0.239	0.264	0.296	0.541	2.479
Pregnant women					
M-DZ	0.012	0.021	0.033	0.058	0.180
M-PA	0.024	0.039	0.062	0.104	0.341
M-PH	0.061	0.095	0.155	0.242	0.846
D-DZ	0.036	0.108	0.156	0.426	0.711
D-PA	0.048	0.129	0.191	0.461	0.872
D-PH	0.085	0.187	0.298	0.576	1.377
Children					
M-DZ	0.011	0.067	0.125	0.203	0.226
M-PA	0.021	0.120	0.246	0.362	0.413
M-PH	0.052	0.283	0.625	0.880	1.042
D-DZ	0.042	0.282	0.471	1.058	2.501
D-PA	0.052	0.332	0.523	1.229	2.633
D-PH	0.083	0.519	1.014	1.714	3.045
Farmers					
M-DZ	0.056	0.120	0.184	6.058	11.931
M-PA	0.105	0.236	0.368	12.258	24.149
M-PH	0.262	0.623	0.984	31.730	62.475
D-DZ	0.259	0.278	0.297	6.208	12.118
D-PA	0.308	0.394	0.481	12.408	24.336
D-PH	0.465	0.781	1.097	31.880	62.662

*M-DZ, Malathion-Diazinon; M-PA, Malathion-Parathion; M-PH, Malathion-Phorate; D-DZ, Dimethoate-Diazinon; D-PA, Dimethoate-Parathion; D-PH, Dimethoate-Phorate.

pesticides. Besides urine, hair has also been proved to differentiate occupational from environmental exposure and provide comparable results. This would render hair an attractive matrix for biomonitoring of pesticides.

Literature data about adverse health effects of OPs in humans are contradictory indicating the need for further research. Several studies report that exposure to OPs is linked with behavioral problems and mental development in children, duration of gestation, infant development, hormone alterations, reduced sperm quality, obesity and cardiometric health.

On summarizing exposure data from OPs, a tendency for reduction or at least a steady exposure was found since 1998. Daily intake was calculated based on biomonitoring data and expressed as malathion, diazinon, parathion, phorate and dimethoate equivalents, for general population, pregnant women, children and farmers. HQ based on ADI reference values was calculated for each OP for the evaluation of the calculated EDIs. Higher exposure was calculated for farmers, median EDIs for the five OPs varied from 1.08 to 19.72 μg/kg bw/day and they are considered to be safe for exposure to malathion, diazinon or parathion, whereas possible exposure to phorate or dimethoate may pose an increased risk for health. Pregnant women seem to be less exposed than the other population groups and the daily intake rates based on our calculations were considered to be safe for health. On the other hand, children were found to have higher exposure compared to environmentally exposed adults, a result that is in agreement with relevant studies in literature. Estimated exposures for children were mostly within safe levels. Median HQ values for children varied between 0.016 and 0.618, for pregnant women 0.005–0.151, for adults 0.008–0.206 and for farmers 0.009–0.979.

Six hypothetical exposure scenarios were examined to assess the risk for combined exposure to two OPs. Exposure to malathion and diazinon was the safest combination while combined exposure to dimethoate and phorate was the worst scenario in which median HI for general population, pregnant women, children and farmers were 0.296, 0.298, 1.014 and 1.097, respectively. The limitations of this study increase the uncertainty of the calculated HQ and HI values, however it is obvious that there is differentiation between the population groups and the risk varies with exposure to certain compounds. It is suggested that the detected urinary levels of DAPs in biomonitoring studies should be converted to intake of the parent compound to assess the human health risk. Questionnaires and self reported data from the general population are valuable to trace back to the parent compound as well as detection of specific metabolites in urine, based on the reported exposure.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2018.10.047.

References

Abdeen, Z., Berman, T., Azmi, K., Abu Seir, R., Agha, H., Ein-Mor, E., Göen, T., Stein, Y., Richter, E., Calderon-Margalit, R., 2015. Urinary organophosphate metabolite levels in Palestinian pregnant women: results of the Middle East Regional Cooperation Project. Int. J. Environ. Health Res. 26 (3), 254–266. https://doi.org/10.1080/09603123.2015.1109067.

Aprea, C., Terenzoni, B., De Angelis, V., Sciarra, G., Lunghini, L., Borzacchi, G., Vasconi, D., Fani, D., Quercia, A., Salvan, A., Settimi, L., 2004. Evaluation of skin and respiratory doses and urinary excretion of alkylphosphates in workers exposed to dimethoate during treatment of olive trees. Arch. Environ. Contam. Toxicol. 48 (1), 127–134. https://doi.org/10.1007/s00244-004-0073-5.

Arcury, T.A., Grzywacz, Ã.J.G., Davis, S.W., Barr, D.B., Quandt, S.A., 2007b. Organophosphorus pesticide urinary metabolite levels of children in farmworker households in eastern North Carolina. Am. J. Ind. Med. 760, 751–760. 2006. https://doi.org/10.1002/ajim.20354.

Arcury, T.A., Grzywacz, J.G., Barr, D.B., Tapia, J., Chen, H., Quandt, S.A., 2007a. Pesticide urinary metabolite levels of children in eastern North Carolina farmworker households. Environ. Health Perspect. 115 (8), 1254–1260. https://doi.org/10.1289/ehp.9975.

Arcury, T.A., Grzywacz, J.G., Chen, H., Vallejos, Q.M., Galván, L., Whalley, L.E., Isom, S., Barr, D.B., Quandt, S.A., 2009. Variation across the agricultural season in organophosphorus pesticide urinary metabolite levels for Latino farmworkers in eastern North Carolina: project design and descriptive results. Am. J. Ind. Med. 52 (7), 539–550. https://doi.org/10.1002/ajim.20703.

Berman, T., Goldsmith, R., Göen, T., Spungen, J., Novack, L., Levine, H., Amitai, Y., Shohat, T., Grotto, I., 2013. Urinary concentrations of environmental contaminants and phytoestrogens in adults in Israel. Environ. Int. 59, 478–484. http://doi.org/10.1016/j.envint.2013.07.012.

Blanco-Muñoz, J., Morales, M.M., Lacasaña, M., Aguilar-Garduño, C., Bassol, S., Cebrián, M.E., 2010. Exposure to organophosphate pesticides and male hormone profile in floriculturist of the state of Morelos, Mexico. Hum. Reprod. 25 (7), 1787–1795. https://doi.org/10.1093/humrep/deq082.

Bouchard, M.F., Chevrier, J., Harley, K.G., Kogut, K., Vedar, M., Calderon, N., et al., 2011. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ. Health Perspect. 119 (8), 1189–1195. https://doi.org/10.1289/ehp.1003185.

Bouchard, M., Gosselin, N.H., Brunet, R.C., Samuel, O., Dumoulin, M.J., Carrier, G., 2003. A toxicokinetic model of malathion and its metabolites as a tool to assess human exposure and risk through measurements of urinary biomarkers. Toxicol. Sci. 73 (1), 182–194. https://doi.org/10.1093/toxsci/kfg061.

Bradman, A., Whitaker, D., Quirós, L., Castorina, R., Claus Henn, B., Nishioka, M., Morgan, J., Barr, D.B., Harnly, M., Brisbin, J.A., Sheldon, L.S., Mckone, T.E., Eskenazi, B., 2007. Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. J. Expo. Sci. Environ. Epidemiol. 17 (4), 331–349. https://doi.org/10.1038/sj.jes.7500507.

Castorina, R., Bradman, A., McKone, T.E., Barr, D.B., Harnly, M.E., Eskenazi, B., 2003. Cumulative organophosphate pesticide exposure and risk assessment among pregnant

women living in an agricultural community: a case study from the CHAMACOS cohort. Environ. Health Perspect. 111 (13), 1640–1648. https://doi.org/10.1289/ehp.5887.
Cecchi, A., Rovedatti, M.G., Sabino, G., Magnarelli, G.G., 2012. Environmental exposure to organophosphate pesticides: assessment of endocrine disruption and hepatotoxicity in pregnant women. Ecotoxicol. Environ. Saf. 80, 280–287. https://doi.org/10.1016/j.ecoenv.2012.03.008.
Chambers, J.E., Carr, R.L., 1995. Biochemical mechanisms contributing to species differences in insecticidal toxicity. Toxicology 105, 291–304.
Christia, C., Bizani, E., Christophoridis, C., Fytianos, K., 2015. Environ. Sci. Pollut. Control Ser. 22 (17), 13167–13178. http://doi.org/10.1007/s11356-015-4456-0.
Clune, A.L., Ryan, P.B., Barr, D.B., 2012. Have regulatory efforts to reduce organophosphorus insecticide exposures been effective? Environ. Health Perspect. 120 (4), 521–525. https://doi.org/10.1289/ehp.1104323.
Colosio, C., Tiramani, M., Maroni, M., 2003. Neurobehavioral effects of pesticides: state of the art. Neurotoxicology 24 (4–5), 577–591. https://doi.org/10.1016/S0161-813X(03)00055-X.
Colosio, C., Tiramani, M., Brambilla, G., Colombi, A., Moretto, A., 2009. Neurobehavioural effects of pesticides with special focus on organophosphorus compounds: which is the real size of the problem? Neurotoxicology 30 (6), 1155–1161. https://doi.org/10.1016/j.neuro.2009.09.001.
Curl, C.L., Beresford, S.A.A., Fenske, R.A., Fitzpatrick, A.L., Lu, C., Nettleton, J.A., Kaufman, J.D., 2015. Estimating pesticide exposure from dietary intake and organic food choices: the Multi-Ethnic Study of Atherosclerosis (MESA). Environ. Health Perspect. 123 (5), 475–483. https://doi.org/10.1289/ehp.1408197.
Curwin, B.D., Hein, M.J., Sanderson, W.T., Striley, C., Heederik, D., Kromhout, H., Reynolds, S.J., Alavanja, M.C., 2007. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. Ann. Occup. Hyg. 51 (1), 53–65. https://doi.org/10.1093/annhyg/mel062.
Dalvie, M.A., Naik, I., Channa, K., London, L., 2011. Urinary dialkyl phosphate levels before and after first season chlorpyrifos spraying amongst farm workers in the Western Cape, South Africa. J. Environ. Sci. Health - Part B Pesticides, Food Contam. Agric. Wastes 46 (2), 163–172. https://doi.org/10.1080/03601234.2011.535384.
Davis, M.D., Wade, E.L., Restrepo, P.R., Roman-Esteva, W., Bravo, R., Kuklenyik, P., Calafat, A.M., 2013. Semi-automated solid phase extraction method for the mass spectrometric quantification of 12 specific metabolites of organophosphorus pesticides, synthetic pyrethroids, and select herbicides in human urine. J. Chromatogr. B: Anal. Tech. Biomed. Life Scie. 929, 18–26. https://doi.org/10.1016/j.jchromb.2013.04.005.
de Gavelle, E., de Lauzon-Guillain, B., Charles, M.A., Chevrier, C., Hulin, M., Sirot, V., Merlo, M., Nougadère, A., 2016. Chronic dietary exposure to pesticide residues and associated risk in the French ELFE cohort of pregnant women. Environ. Int. 92 (93), 533–542. https://doi.org/10.1016/j.envint.2016.04.007.
Dewalque, L., Charlier, C., Pirard, C., 2014. Estimated daily intake and cumulative risk assessment of phthalate diesters in a Belgian general population. Toxicol. Lett. 231 (2), 161–168. https://doi.org/10.1016/j.toxlet.2014.06.028.
Ding, G., Han, S., Wang, P., Gao, Y., Shi, R., Wang, G., Tian, Y., 2012. Increased levels of 8-hydroxy-2′-deoxyguanosine are attributable to organophosphate pesticide exposure among young children. Environ. Pollut. 167, 110–114. https://doi.org/10.1016/j.envpol.2012.04.001.
Dirtu, A.C., Geens, T., Dirinck, E., Malarvannan, G., Neels, H., Van Gaal, L., et al., 2013. Phthalate metabolites in obese individuals undergoing weight loss: Urinary levels and estimation of the phthalates daily intake. Envir. Int. 59, 344–353. https://doi.org/10.1016/j.envint.2013.06.023.
EFSA, 2013. International Frameworks dealing with human risk assessment on combined exposure to multiple chemicals. EFSA J. 11 (7), 3313 2013.
Eskenazi, B., Marks, A.R., Bradman, A., Harley, K., Barr, D.B., Johnson, C., Morga, N., Jewell, N.P., 2007. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ. Health Perspect. 115 (5), 792–798. https://doi.org/10.1289/ehp.9828.
Fosu, P.O., Donkor, A., Ziwu, C., Dubey, B., Kingsford-Adaboh, R., Asante, I., Nyarko, S., Tawiah, R., Nazzah, N., 2017. Surveillance of pesticide residues in fruits and vegetables from Accra Metropolis markets, Ghana, 2010-2012: a case study in Sub-Saharan Africa. Environ. Sci. Pollut. Control Ser. https://doi.org/10.1007/s11356-017-9287-8. 2010–2012.
Gad Alla, S.A., Loutfy, N.M., Shendy, A.H., Ahmed, M.T., 2015. Hazard index, a tool for a long term risk assessment of pesticide residues in some commodities, a pilot study. Regul. Toxicol. Pharmacol. 73 (3), 985–991. https://doi.org/10.1016/j.yrtph.2015.09.016.
Garfitt, S.J., Jones, K., Mason, H.J., Cocker, J., 2002. Exposure to the organophosphate diazinon: data from a human volunteer study with oral and dermal doses. Toxicol. Lett. 134 (1–3), 105–113. https://doi.org/10.1016/S0378-4274(02)00178-9.
Gunier, R.B., Bradman, A., Harley, K.G., Kogut, K., Eskenazi, B., 2016. Prenatal residential proximity to agricultural pesticide use and IQ in 7-year-old children. Environ. Health Perspect (May). https://doi.org/10.1289/EHP504.
Guodong, D., Pei, W., Ying, T., Jun, Z., Yu, G., Xiaojin, W., Rong, S., Guoquan, W., Xiaoming, S., 2012. Organophosphate pesticide exposure and neurodevelopment in young shanghai children. Environ. Sci. Technol. 46 (5), 2911–2917. https://doi.org/10.1021/es202583d.
Hardy, E.M., Duca, R.C., Salquebre, G., Appenzeller, B.M.R., 2015. Multi-residue analysis of organic pollutants in hair and urine for matrices comparison. Forensic Sci. Int. 249, 6–19. https://doi.org/10.1016/j.forsciint.2014.12.003.
Harley, K.G., Engel, S.M., Vedar, M.G., Eskenazi, B., Whyatt, R.M., Lanphear, B.P., Bradman, A., Rauh, V.A., Yolton, K., Hornung, R.W., Wetmur, J.G., Chen, J., Holland, N.T., Barr, D.B., Perera, F., Wolff, M.S., 2016. Prenatal exposure to organophosphorous pesticides and fetal growth: pooled results from four longitudinal birth cohort studies. Environ. Health Perspect. 124 (7), 1084–1092. https://doi.org/10.1289/ehp.1409362.
Harley, K.G., Huen, K., Schall, R.A., Holland, N.T., Bradman, A., Barr, D.B., Eskenazi, B., 2011. Association of organophosphate pesticide exposure and paraoxonase with birth outcome in mexican-american women. PloS One 6 (8). https://doi.org/10.1371/journal.pone.0023923.
Heffernan, A., English, K., Toms, L., Calafat, A., Valentin-Blasini, L., Hobson, P., Broomhall, S., Ware, R.S., Jagals, P., Sly, P.D., Mueller, J., 2016. Cross-sectional biomonitoring study of pesticide exposures in Queensland, Australia, using pooled urine samples. Environ. Sci. Pollut. Control Ser. 23 (23), 23436–23448. https://doi.org/10.1007/s11356-016-7571-7.
Hernández, A.F., Tsatsakis, A.M., 2017. Human exposure to chemical mixtures: challenges for the integration of toxicology with epidemiology data in risk assessment. Food Chem. Toxicol. 103, 188–193. https://doi.org/10.1016/j.fct.2017.03.012.
Heudorf, U., Angerer, J., Drexler, H., 2004. Current internal exposure to pesticides in children and adolescents in Germany: urinary levels of metabolites of pyrethroid and organophosphorus insecticides. Int. Arch. Occup. Environ. Health 77 (1), 67–72. https://doi.org/10.1007/s00420-003-0470-5.
Hoffmann, U., Papendorf, T., 2006. Organophosphate poisonings with parathion and dimethoate. Intensive Care Med. 32 (3), 464–468. https://doi.org/10.1007/s00134-005-0051-z.
Institute of Medicine, 1998. Dietary Reference Intakes: a Risk Assessment Model for Establishing Upper Intake Levels for Nutrients. The National Academies Press, Washington, DC. https://doi.org/10.17226/6432.
IPCS INCHEM http://www.inchem.org/documents/pims/chemical/pimg001.htm.
JMPR, 2000. PARATHION. Report of the 2000 JMPR FAO/WHO Meeting of Experts.
JMPR, 2003. DIMETHOATE (Addendum). In: Marrs T.C. Joint FAO/WHO Meeting on Pesticide Residues. Pfeil, R, pp. 85–100.
JMPR, 2004. PHORATE. First Draft Prepared by P.K. Gupta Toxicology Consulting Services Inc, Rajinder Nagar, Bareilly, Uta Pradesh, India, pp. 171–205.
JMPR, 2005. PHORATE. In: FAO Report 12. pp. 297–299.
JMPR, 2006. DIAZINON (Addendum). In: Mueller, U. And Solecki, R. Joint FAO/WHO Meeting on Pesticide Residues.
JMPR, 2016. MALATHION. In: Joint FAO/WHO Meeting on Pesticide Residues in Food. Report 2016.
Jones, K., Everard, M., Harding, A.H., 2014. Investigation of gastrointestinal effects of organophosphate and carbamate pesticide residues on young children. Int. J. Hyg Environ. Health 217 (2–3), 392–398. https://doi.org/10.1016/j.ijheh.2013.07.015.
Katsikantami, I., Sifakis, S., Tzatzarakis, M.N., Vakonaki, E., Kalantzi, O.-I., Tsatsakis, A.M., Rizos, A.K., 2016. A global assessment of phthalates burden and related links to health effects. Environ. Int. 97, 212–236. https://doi.org/10.1016/j.envint.2016.09.013.
Kavvalakis, M.P., Tzatzarakis, M.N., Theodoropoulou, E.P., Barbounis, E.G., Tsakalof, A.K., Tsatsakis, A.M., 2013. Development and application of LC-APCI-MS method for biomonitoring of animal and human exposure to imidacloprid. Chemosphere 93 (10), 2612–2620. https://doi.org/10.1016/j.chemosphere.2013.09.087.
Kissel, J.C., Curl, C.L., Kedan, G., Lu, C., Griffith, W., Barr, D.B., Needham, L.L., Fenske, R.A., 2005. Comparison of organophosphorus pesticide metabolite levels in single and multiple daily urine samples collected from preschool children in Washington State. J. Expo. Anal. Environ. Epidemiol. 15 (2), 164–171. https://doi.org/10.1038/sj.jea.7500384.
Knipe, D.W., Jayasumana, C., Siribaddana, S., Priyadarshana, C., Pearson, M., Gunnell, D., Metcalfe, C., Tzatzarakis, M.N., Tsatsakis, A.M., 2016. Feasibility of hair sampling to assess levels of organophosphate metabolites in rural areas of Sri Lanka. Environ. Res. 147, 207–211. http://doi.org/10.1016/j.envres.2016.02.011.
Koch, H.M., Hardt, J., Angerer, J., 2001. Biological monitoring of exposure of the general population to the organophosphorus pesticides chlorpyrifos and chlorpyrifos-methyl by determination of their specific metabolite 3,5,6-trichloro-2-pyridinol. Int. J. Hyg Environ. Health 204 (2–3), 175–180. https://doi.org/10.1078/1438-4639-00082.
Kokkinaki, A., Kokkinakis, M., Kavvalakis, M.P., Tzatzarakis, M.N., Alegakis, A.K., Maravgakis, G., Babatsikou, F., Fragkiadakis, G.A., Tsatsakis, A.M., 2014. Biomonitoring of dialkylphosphate metabolites (DAPs) in urine and hair samples of sprayers and rural residents of Crete, Greece. Environ. Res. 134, 181–187. https://doi.org/10.1016/j.envres.2014.07.012.
Kongtip, P., Nankongnab, N., Woskie, S., Phamonphon, A., Tharnpoophasiam, P., Wilaiwan, K., Srasom, P., 2014. Organophosphate urinary metabolite levels during pregnancy, delivery and postpartum in women living in agricultural areas in Thailand. J. Occup. Health 55 (5), 367–375.
Koureas, M., Tsakalof, A., Tzatzarakis, M., Vakonaki, E., Tsatsakis, A., Hadjichristodoulou, C., 2014. Biomonitoring of organophosphate exposure of pesticide sprayers and comparison of exposure levels with other population groups in Thessaly (Greece). Occup. Environ. Med. 71 (2), 126–133. https://doi.org/10.1136/oemed-2013-101490.
Koutroulakis, D., Sifakis, S., Tzatzarakis, M.N., Alegakis, A.K., Theodoropoulou, E., Kavvalakis, M.P., Kappou, D., Tsatsakis, A.M., 2014. Dialkyl phosphates in amniotic fluid as a biomarker of fetal exposure to organophosphates in Crete, Greece; association with fetal growth. Reprod. Toxicol. 46, 98–105. https://doi.org/10.1016/j.reprotox.2014.03.010.
Krieger, R., Thongsinthusak, T., 1993. Metabolism and excretion of dimethoate following ingestion of overtolerance peas and a bolus dose. Food Chem. Toxicol. 31 (3), 177–182.
Lambert, W.E., Lasarev, M., Muniz, J., Scherer, J., Rothlein, J., Santana, J., McCauley, L., 2005. Variation in organophosphate pesticide metabolites in urine of children living in agricultural communities. Environ. Health Perspect. 113 (4), 504–508. https://doi.org/10.1289/ehp.6890.
Lewis, R.C., Cantonwine, D.E., Anzalota Del Toro, L.V., Calafat, A.M., Valentin-Blasini, L.,

Davis, M.D., Montesano, M.A., Alshawabkeh, A.N., Cordero, J.,F., Meeker, J.D., 2015. Distribution and determinants of urinary biomarkers of exposure to organophosphate insecticides in Puerto Rican pregnant women. Sci. Total Environ. 512–513, 337–344. https://doi.org/10.1016/j.scitotenv.2015.01.059.

Lu, C., Bravo, R., Caltabiano, L.M., Irish, R.M., Weerasekera, G., Barr, D.B., 2005. The presence of dialkylphosphates in fresh fruit juices: implication for organophosphorus pesticide exposure and risk assessments. J. Toxicol. Environ. Health 68 (3), 209–227.

Lu, C., Barr, D.B., Pearson, M.A., Waller, L.A., 2008. Dietary intake and its contribution to longitudinal organophosphorus pesticide exposure in urban/suburban children. Environ. Health Perspect. 116 (4), 537–542. https://doi.org/10.1289/ehp.10912.

Margariti, M.G., Tsatsakis, A.M., 2009. Analysis of dialkyl phosphate metabolites in hair using gas chromatography-mass spectrometry: a biomarker of chronic exposure to organophosphate pesticides. In: Biomarkers: Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals, 14(November)pp. 137–147. https://doi.org/10.1080/13547500902792912.

Melgarejo, M., Mendiola, J., Koch, H.M., Monino-Garcia, M., Noguera-Velasco, J.A., Torres-Cantero, A.M., 2015. Associations between urinary organophosphate pesticide metabolite levels and reproductive parameters in men from an infertility clinic. Environ. Res. 137, 292–298. https://doi.org/10.1016/j.envres.2015.01.004.

Melnyk, L.J., Xue, J., Brown, G.G., McCombs, M., Nishioka, M., Michael, L.C., 2014. Dietary intakes of pesticides based on community duplicate diet samples. Sci. Total Environ. 468–469, 785–790. https://doi.org/10.1016/j.scitotenv.2013.08.101.

Michalakis, M., Tzatzarakis, M.N., Kovatsi, L., Alegakis, A.K., Tsakalof, A.K., Heretis, I., Tsatsakis, A., 2014. Hypospadias in offspring is associated with chronic exposure of parents to organophosphate and organochlorine pesticides. Toxicol. Lett. 230 (2), 139–145. https://doi.org/10.1016/j.toxlet.2013.10.015.

Morgan, D.P., Hetzler, H.L., Slach, E.F., Lin, L.I., 1977. Urinary excretion of para-nitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. Arch. Environ. Contam. Toxicol. 6 (2–3), 159–173. Retrieved from. http://www.ncbi.nlm.nih.gov/pubmed/900999.

Morgan, M.K., Jones, P.A., 2013. Dietary predictors of young children's exposure to current-use pesticides using urinary biomonitoring. Food Chem. Toxicol. 62, 131–141. https://doi.org/10.1016/j.fct.2013.08.029.

Motsoeneng, P.M., Dalvie, M.A., 2015. Relationship between urinary pesticide residue levels and neurotoxic symptoms among women on farms in the western cape, South Africa. Int. J. Environ. Res. Publ. Health 12 (6), 6281–6299. https://doi.org/10.3390/ijerph120606281.

Myridakis, A., Chalkiadaki, G., Fotou, M., Kogevinas, M., Chatzi, L., Stephanou, E.G., 2016. Exposure of preschool-age Greek children (RHEA cohort) to bisphenol A, parabens, phthalates, and organophosphates. Environ. Sci. Technol. 50 (2), 932–941. https://doi.org/10.1021/acs.est.5b03736.

Naeher, L.P., Tulve, N.S., Egeghy, P.P., Barr, D.B., Adetona, O., Fortmann, R.C., Needham, L.L., Bozeman, E., Aaron Hilliard Sheldon, L.S., 2010. Organophosphorus and pyrethroid insecticide urinary metabolite concentrations in young children living in a southeastern United States city. Sci. Total Environ. 408 (5), 1145–1153. https://doi.org/10.1016/j.scitotenv.2009.10.022.

Naksen, W., Prapamontol, T., Mangklabruks, A., Chantara, S., Thavornyutikarn, P., Srinual, N., Parinya Panuwet, P., Ryan, P.B., Riederer, A.M., Barr, D.B., 2015. Associations of maternal organophosphate pesticide exposure and PON1 activity with birth outcomes in SAWASDEE birth cohort, Thailand. Environ. Res. 142, 288–296. https://doi.org/10.1016/j.envres.2015.06.035.

Osaka, A., Ueyama, J., Kondo, T., Nomura, H., Sugiura, Y., Saito, I., Nakane, K., Takaishi, A., Ogi, H., Wakusawa, S., Ito, Y., Kamijima, M., 2016. Exposure characterization of three major insecticide lines in urine of young children in Japan-neonicotinoids, organophosphates, and pyrethroids. Environ. Res. 147, 89–96. https://doi.org/10.1016/j.envres.2016.01.028.

Oulhote, Y., Bouchard, M.F., 2013. Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children. Environ. Health Perspect. 121 (11–12), 1378–1384. https://doi.org/10.1289/ehp.1306667.

Oya, N., Ito, Y., Hioki, K., Asai, Y., Aoi, A., Sugiura, Y., Ueyama, J., Oguri, T., Kato, S., Ebara, T., Kamijima, M., 2016. Quantitative analysis of organophosphate insecticide metabolites in urine extracted from disposable diapers of toddlers in Japan. Int. J. Hyg Environ. Health. https://doi.org/10.1016/j.ijheh.2016.10.009.

Panuwet, P., Prapamontol, T., Chantara, S., Barr, D.B., 2009. Urinary pesticide metabolites in school students from northern Thailand. Int. J. Hyg Environ. Health 212 (3), 288–297. https://doi.org/10.1016/j.ijheh.2008.07.002.

Payne-Sturges, D., Cohen, J., Castorina, R., Axelrad, D.A., Woodruff, T.J., 2009. Evaluating cumulative organophosphorus pesticide body burden of children: a national case study. Environ. Sci. Technol. 43 (20), 7924–7930. https://doi.org/10.1021/es900713s.

Perry, M.J., Venners, S.A., Barr, D.B., Xu, X., 2007. Environmental pyrethroid and organophosphorus insecticide exposures and sperm concentration. Reprod. Toxicol. 23 (1), 113–118. https://doi.org/10.1016/j.reprotox.2006.08.005.

Phung, D.T., Connell, D., Miller, G., Hodge, M., Patel, R., Cheng, R., Abeyewardene, M., Chu, C., 2012. Biological monitoring of chlorpyrifos exposure to rice farmers in Vietnam. Chemosphere 87 (4), 294–300. https://doi.org/10.1016/j.chemosphere.2011.11.075.

Raanan, R., Harley, K.G., Balmes, J.R., Bradman, A., Lipsett, M., Eskenazi, B., 2015. Early-life exposure to organophosphate pesticides and pediatric respiratory symptoms in the CHAMACOS cohort. Environ. Health Perspect. 123 (2), 179–185. http://doi.org/10.1289/ehp.1408235.

Ranjbar, M., Rotondi, M.A., Ardern, C.I., Kuk, J.L., 2015. The influence of urinary concentrations of organophosphate metabolites on the relationship between BMI and cardiometabolic health risk. J. Obesity 2015. https://doi.org/10.1155/2015/687914.

Rastogi, S.K., Satyanarayan, P.V.V., Ravishankar, D., Tripathi, S., 2009. A study on oxidative stress and antioxidant status of agricultural workers exposed to organophosphorus insecticides during spraying. Indian J. Occup. Environ. Med. 13 (3), 131–134. https://doi.org/10.4103/0019-5278.58916.

Rauch, S.A., Braun, J.M., Barr, D.B., Calafat, A.M., Khoury, J., Montesano, M.A., 2012. Associations of prenatal exposure to organophosphate pesticide metabolites with gestational age and birth weight. Environ. Health Perspect. 120 (7), 1055–1061. https://doi.org/10.1289/ehp.1104615.

Roca, M., Miralles-Marco, A., Ferre, J., Perez, R., Yusa, V., 2014. Biomonitoring exposure assessment to contemporary pesticides in a school children population of Spain. Environ. Res. 131, 77–85. https://doi.org/10.1016/j.envres.2014.02.009.

Rothlein, J., Rohlman, D., Lasarev, M., Phillips, J., Muniz, J., McCauley, L.A., 2006. Organophosphate pesticide exposure and neurobehavioral performance in agricultural and nonagricultural Hispanic workers. Environ. Health Perspect. 114 (5), 691–696. https://doi.org/10.1289/ehp.8182.

Sexton, K., 2012. Cumulative risk assessment: an overview of methodological approaches for evaluating combined health effects from exposure to multiple environmental stressors. Int. J. Environ. Res. Publ. Health 9, 370–390. https://doi.org/10.3390/ijerph9020370.

Shapiro, G.D., Dodds, L., Arbuckle, T.E., Ashley-Martin, J., Ettinger, A.S., Fisher, M., Taback, S., Bouchard, M.F., Monnier, P., Dallaire, R., Morisset, A.-S., Fraser, W., 2016. Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: the MIREC Study. Environ. Res. 147, 71–81. https://doi.org/10.1016/j.envres.2016.01.040.

Shomar, B., Al-Saad, K., Nriagu, J., 2014. Mishandling and exposure of farm workers in Qatar to organophosphate pesticides. Environ. Res. 133, 312–320. https://doi.org/10.1016/j.envres.2014.06.010.

Sokoloff, K., Fraser, W., Arbuckle, T.E., Fisher, M., Gaudreau, E., LeBlanc, A., Morisset, A.-S., Bouchard, M.F., 2016. Determinants of urinary concentrations of dialkyl phosphates among pregnant women in Canada - results from the MIREC study. Environ. Int. 94, 133–140. http://doi.org/10.1016/j.envint.2016.05.015.

Tsakiris, I.N., Goumenou, M., Tzatzarakis, M.N., Alegakis, A.K., Tsitsimpikou, C., Ozcagli, E., Vynias, D., Tsatsakis, A.M., 2015. Risk assessment for children exposed to DDT residues in various milk types from the Greek market. Food Chem. Toxicol. 75, 156–165. http://doi.org/10.1016/j.fct.2014.11.012.

Tsatsakis, A.M., Androutsopoulos, V.P., Zafiropoulos, A., Babatsikou, F., Alegakis, A., Dialyna, I., Tzatzarakis, M., Koutis, C., 2011. Association of xenobiotic-metabolizing enzyme-genotypes PON1Q192R, PON1L55M and CYP1A1*2A MSPI with pathological symptoms of a rural population in south Greece. Xenobiotica 41 (10), 914–925.

Tsatsakis, A.M., Docea, A.O., Tsitsimpikou, C., 2016. New challenges in risk assessment of chemicals when simulating real exposure scenarios; simultaneous multi-chemicals' low dose exposure. Food Chem. Toxicol. 96, 174–176. https://doi.org/10.1016/j.fct.2016.08.011.

Tsatsakis, A.M., Kouretas, D., Tzatzarakis, M.N., Stivaktakis, P., Tsarouhas, K., Golokhvast, K.S., Rakitskii, V.N., Tutelyan, V.A., Hernandez, A.F., Rezaee, R., Chung, G., Fenga, C., Engin, A.B., Neagu, M., Arsene, A.L., Docea, A.O., Gofita, E., Calina, D., Taitzoglou, I., Liesivuori, J., Hayes, A.W., Gutnikov, S., Tsitsimpikou, C., 2017. Simulating real-life exposures to uncover possible risks to human health: a proposed consensus for a novel methodological approach. Hum. Exp. Toxicol. 36 (6), 554–564. https://doi.org/10.1177/0960327116681652.

Tsatsakis, A.M., Tsakiris, I.N., Tzatzarakis, M.N., Agourakis, Z.B., Tutudaki, M., Alegakis, A.K., 2003. Three-year study of fenthion and dimethoate pesticides in olive oil from organic and conventional cultivation. Food Addit. Contam. 20 (6), 553–559. http://doi.org/10.1080/0265203031000070786.

Tsatsakis, A.M., Zafiropoulos, A., Tzatzarakis, M., Tzanakakis, G.N., Kafatos, A., 2009. Relation of PON1 and CYP1A1 genetic polymorphisms to clinical findings in a cross-sectional study of a Greek population professionally exposed to pesticides. Toxicol. Lett. 186 (1), 66–72.

Tuomainen, A., Kangas, J.A., Meuling, W.J.A., Glass, R.C., 2002. Monitoring of pesticide applicators for potential dermal exposure to malathion and biomarkers in urine. Toxicol. Lett. 134 (1–3), 125–132. https://doi.org/10.1016/S0378-4274(02)00181-9.

Ueyama, J., Saito, I., Takaishi, A., Nomura, H., Inoue, M., Osaka, A., Sugiura, Y., Hayashi, Y., Wakusawa, S., Ogi, H., Inuzuka, K., Kamijima, M., Kondo, T., 2014. A revised method for determination of dialkylphosphate levels in human urine by solid-phase extraction and liquid chromatography with tandem mass spectrometry: application to human urine samples from Japanese children. Environ. Health Prev. Med. 19 (6), 405–413. https://doi.org/10.1007/s12199-014-0407-5.

US EPA, 2013. Recognition and Management of Pesticide Poisoning, sixth ed. (Chapter 5), Organophosphates. https://www.epa.gov/sites/production/files/documents/rmpp_6thed_ch5_organophosphates.pdf (September 2017).

Valcke, M., Samuel, O., Bouchard, M., Dumas, P., Belleville, D., Tremblay, C., 2006. Biological monitoring of exposure to organophosphate pesticides in children living in peri-urban areas of the Province of Quebec, Canada. Int. Arch. Occup. Environ. Health 79 (7), 568–577. https://doi.org/10.1007/s00420-006-0085-8.

Wang, P., Tian, Y., Wang, X.-J., Gao, Y., Shi, R., Wang, G.-Q., Hu, G.-H., Shen, X.-M., 2012. Organophosphate pesticide exposure and perinatal outcomes in Shanghai, China. Environ. Int. 42, 100–104. https://doi.org/10.1016/j.envint.2011.04.015.

WHO, 2006. Guidelines for Drinking-water Quality. First Addendum to Third Edition, vol. 1 World Health Organization, Geneva.

Wigle, D.T., Turner, M.C., Krewski, D., 2009. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. Environ. Health Perspect. 117 (10), 1505–1513. https://doi.org/10.1289/ehp.0900582.

Ye, M., Beach, J., Martin, J.W., Senthilselvan, A., 2015. Associations between dietary factors and urinary concentrations of organophosphate and pyrethroid metabolites in a Canadian general population. Int. J. Hyg Environ. Health 218 (7), 616–626.

https://doi.org/10.1016/j.ijheh.2015.06.006.
Ye, M., Beach, J., Martin, J.W., Senthilselvan, A., 2016. Urinary dialkyl phosphate concentrations and lung function parameters in adolescents and adults: results from the canadian health measures Survey. Environ. Health Perspect. 124 (4), 491–497. https://doi.org/10.1289/ehp.1509745.
Ye, X., Pierik, F.H., Hauser, R., Duty, S., Angerer, J., Park, M.M., Burdorf, A., Hofmanh, A., Jaddoe, V.W.V., Mackenbach, J.P., Steegers, E.A.P., Tiemeier, H., Longnecker, M.P., 2008. Urinary metabolite concentrations of organophosphorous pesticides, bisphenol A, and phthalates among pregnant women in Rotterdam, The Netherlands: the Generation R study. Environ. Res. 108 (2), 260–267. https://doi.org/10.1016/j.envres.2008.07.014.
Yolton, K., Xu, Y., Sucharew, H., Succop, P., Altaye, M., Popelar, A., Montesano, M.A., Calafat, A.M., Khoury, J.C., 2013. Impact of low-level gestational exposure to organophosphate pesticides on neurobehavior in early infancy: a prospective study. Environ. Health: A Global Acc. Sci. Source 12 (1), 79. https://doi.org/10.1186/1476-069X-12-79.
Zaganas, I., Kapetanaki, S., Mastorodemos, V., Kanavouras, K., Colosio, C., Wilks, M.F., Tsatsakis, A.M., 2013. Linking pesticide exposure and dementia: what is the evidence? Toxicology 307, 3–11. https://doi.org/10.1016/j.tox.2013.02.002.
Zentai, A., Szabó, I.J., Kerekes, K., Ambrus, Á., 2016. Risk assessment of the cumulative acute exposure of Hungarian population to organophosphorus pesticide residues with regard to consumers of plant based foods. Food Chem. Toxicol. 89, 67–72. https://doi.org/10.1016/j.fct.2016.01.016.
Zhang, Y., Gao, Y., Shi, R., Chen, D., Wang, X., Kamijima, M., Sakai, K., Nakajima, T., Khalequzzaman, Md, Zhou, Y., Zheng, Y., Bao, P., Tian, Y., 2015. Household pesticide exposure and the risk of childhood acute leukemia in Shanghai, China. Environ. Sci. Pollut. Control Ser. 22 (15), 11755–11763. https://doi.org/10.1007/s11356-015-4362-5.
Zhang, Y., Han, S., Liang, D., Shi, X., Wang, F., Liu, W., Zhang, L., Chen, L., Gu, Y., Tian, Y., 2014. Prenatal exposure to organophosphate pesticides and neurobehavioral development of neonates: a birth cohort study in Shenyang, China. PloS One 9 (2), e88491. https://doi.org/10.1371/journal.pone.0088491.