HUMAN RISK ASSESSMENT: TOXICITY ISSUES AND CHALLENGES ASSOCIATED WITH MIXTURE OF CHEMICALS RELEASED DURING PLASTIC REUSE AND RECYCLING

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Abstract

The objective of study is to understand challenges in assessing risk due to exposures of mixture of polymers released into water during reuse and recycling activities of plastic materials on human health. A four- step human health risk assessment framework consist of hazard identification, dose response assessment, risk estimation, uncertainty characterization was developed for assessing risk. Mixture of Bisphenol A (BPA) and Di (2-ethylhexyl) phthalate (DEHP): endocrine disrupting substances was taken as an example. Both of these chemicals are used in packaging bottles, beverage and food containers and are probable to occur in water cycle simultaneously, and thus, assessment of their combined risk is required. Information on co-occurrence of these chemicals in water medium, their associated toxic effects to human were obtained from published reports and current knowledge gaps were identified. Findings of this study indicated that there exists data gaps in (1) lack of information on simultaneous exposure of two chemicals, (2) their combined mode of action, (3) mixture toxicity dose and concentration dose- response relationships, (4) lack of knowledge about interaction of chemicals (5) variation of exposure with time and location, (6) complex effects at different level and segments of community, including indirect effects on ecosystem. These identified data gaps need to be filled by conducting more research in this direction so that exposure of population to polymeric compounds and chemicals in water from plastic waste can be estimated with more confidence and efforts for protecting them can be made. This information is required in properly understanding toxic effects of mixture of plastic compounds on human health.

Keywords: Plastics; mixture; health risk; toxicity

1. Introduction

Plastic has become inevitable part of human life. Plastics are used in packaging, electronics, sports, transportation, medicine, and in all other kind of industries. They are increasingly getting accumulated into environment and are in fact virtually present inside human as well. Plastics are made up of many chemicals such as Phthalate, Polybrominated biphenyls, Bisphenol-A, Cadmium which are released during plastic manufacturing and leaching of plastics from various plastic products[1]. Current use of plastic is not sustainable as inferred by release of harmful endocrine disrupting substances like Bisphenol-A(BPA) and Di-(2-ethylhexyl)(DEHP) phthalate from plastics reuse and recycling[2]. BPA is used in polycarbonate plastic and epoxy resins,

plastic consumer products like toys, water pipes, food container, infant feeding bottles and other products. BPA exposure has shown many adverse outcomes to children and adults including reproductive and developmental effects [3]. DEHP is used as plasticizer found in toys, building material, water bottles, flooring, and medical products. Research also indicates that DEHP has adverse effect on liver, reproductive tract, kidney and lungs [4]. Many studies have been conducted to understand risk of individual chemicals— BPA or DEHP on human health and ecology [5][6][7]. These studies suggest that chemicals cause adverse impact on human health through various exposure routes directly or indirectly. Though various scientific studies have shown severe effects on human of individual chemicals, there is not much known about risk to human, from exposure to mixture of endocrine disrupting chemicals originating from plastics. Some studies have monitored release of BPA or DEHP in water Table 1 [8]-[26]; however they have not done comprehensive risk assessment for simultaneous exposure of two or more than two plastic based EDC (Endocrine disrupting chemicals).

The objective of our study was to understand various gaps in literature to conduct risk assessment from exposure of human to mixture of BPA and DEHP. Identification of risk associated with interacting effect of these chemicals on human could help in suggesting actions to address knowledge gaps.

Table 1. Summary of occurrence of BPA and DEHP in surface and drinking water.

Reference	Water type	Concentration Observed (ng/L)	Study type	Location	Leaching conditions
BPA					
Elobeid et al.2012. [8]	Drinking water	7.5	Laboratory	Saudi Arabia	Stored at 40 ºC
Kuch and Ballschmiter, 2001. [9]	Drinking water	0.5-2	Environmental data	Germany	NR
Santhi et al,2012 [10]	Drinking water	3.2±2.6 11.3±5.3	Laboratory	Malaysia	25ºC 50ºC for three days
Sun et al,2000. [11]	Drinking water	0.59±0.04	Laboratory	Japan	Water in contact with bottle for 30 min, 95°C
Toyo'oka and Oshige, 2000[12]	Drinking water	3-10	Laboratory	Japan	NR
Y.-Y.Fan et al,2014. [13]	Drinking water	31	Laboratory	China	70ºC after 4 weeks,3 to 4% leaching
Belfroid et al. (2000). [14]	Surface water	Up to 21000	Environmental data	Netherlands	NR
Boyd et al., 2004[15]	Surface water	9-44	Environmental data	USA	NR
Vanda et al.(2011) [16]	Surface water	18-33	Environmental data	USA	NR
Stasinakis et al.(2012) [17]	Surface water	55-162	Environmental data	Greece	NR
Zhang et al.(2014) [18]	Surface water	8.24-263	Environmental data	China	NR
Zou et al.(2014) [19]	Surface water	ND-920	Environmental data	China	NR

Reference	Water type	Concentration Observed (ng/L)	Study type	Location	Leaching conditions
DEHP					
Leivadara et al. (2008) [20]	Drinking water PET bottle	2000	Laboratory	Greece	24 °C in the dark for 3 months
Schmid et al. (2008) [21]	Drinking water through PET bottle	100-380	Laboratory	Switzerland	34 °C for 17 h under direct sunlight,
Bosnir et al.,(2007) [22]	Mineral water in PET bottles	8780	Laboratory	Croatia	30 Days at 22°C
Cao, (2008) [23]	Water from bottle	220	Laboratory	Canada	NR
Vethaak et al.,2005 [24]	Surface water	320000	Environmental data	Netherlands	NR
Yuan et al. (2002) [25]	Surface water	9300	Environmental data	Taiwan	NR
Yuwatini et al. (2006) [26]	Surface water	8000-25000	Environmental data	Japan	NR

NR—Not reported PET— Polyethylene terephthalate

2. Methodology

A schematic showing the risk assessment process used in this study is given in Fig 1. Human health risk assessment is carried out by four steps— Hazard identification, Exposure assessment, Dose-response assessment, and Risk characterization [27]. Literature review was conducted to obtain different parameters required at every step of risk assessment. BPA and DEHP were used as examples of plastic based EDC to understand the knowledge gaps in assessing mixture toxicity.

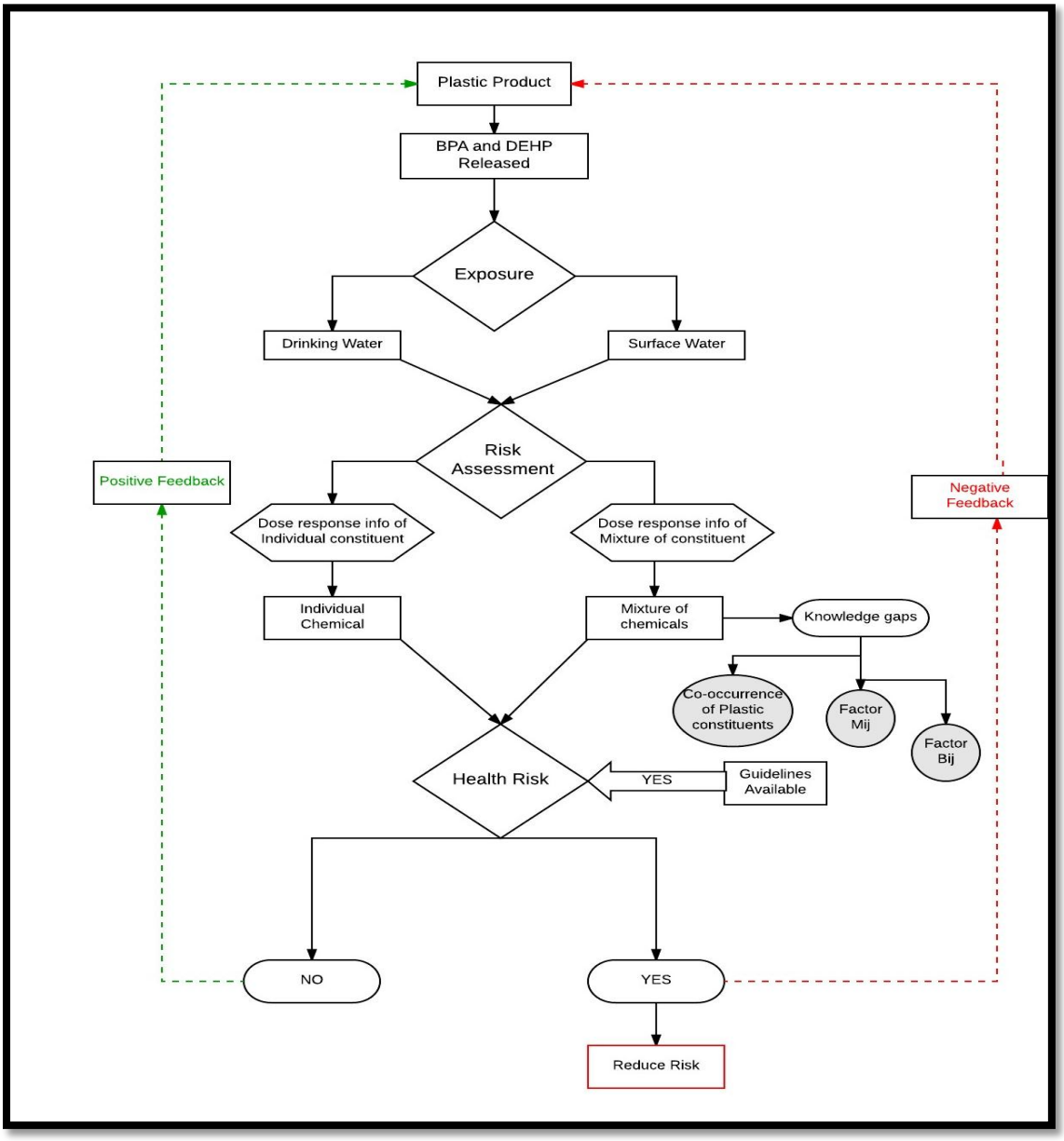

Fig.1 Schematic Showing the Risk Assessment Process

2.1 Hazard Identification

In present study, BPA and DEHP are two chemicals identified as toxins. There is some concern regarding BPA effect on brain, behaviour and prostate glands in fetuses, infants [28].

Based on studies, there is concern for testicular effects, toxicity to kidneys, reproductive effects due to prolonged exposure of DEHP [29]. Toxic kinetics profiles of BPA and DEHP can be understood from studies done on rats, rodents and other animal studies. Both *in vitro* and *in vivo* studies are done to understand metabolism of BPA and DEHP on human [30][31][32]. Both BPA and DEHP alter endocrine system— Phthalates function as anti-androgens while the main action attributed to BPA is oestrogen-like activity [33].

2.2 Exposure Assessment

Scenario description

There are different exposure routes for contaminants including oral, subcutaneous, inhalation, and dietary. Both BPA and DEHP can be released into environment—air, water (surface and groundwater), and soil from wide range of plastic products during reuse and recycling. BPA and DEHP after leaching from the plastic water bottles, result in human exposure through drinking activity and/or swimming activity. These chemicals are also found in environmental field like surface water and can be consumed by people during swimming activities. Hence, exposure route considered in this study is ingestion drinking bottled water or ingestion of water while swimming. It was assumed that BPA and DEHP are released in water from bottle based plastic constituents. Occurrence of BPA and DEHP in drinking water and surface water with their concentrations are shown in Table 1. Co-occurrence of both chemicals simultaneously is shown in Table 2 using information from published studies.

Table 2. Identified information on Co-Occurrence of BPA and DEHP in Drinking and Surface Water from published studies.

Reference	Water type	Concentration BPA(ng/L)	Concentration DEHP(ng/L)	Leaching condition
Casajuan and Lacorte (2003)[34]	Water stored in Bottles	10	134	10 weeks storage, 30°C from PET bottles
Amiridou and Voutsa, (2011)[35]	Drinking Water	170	580	NR
Fromme et al.(2001)[36]	Surface Water	0.5-410	330-97800	NR
Tran et al.(2015)[37]	Surface water (Downstream of WWTP)	110-790	310-1700	NR

WWTP—Wastewater Treatment Plant

Estimation of Average daily dose

Average daily dose is defined by US EPA as— "Dose rate averaged over a pathway-specific period of exposure expressed as a daily dose on a per-unit-body-weight basis". Amount of leaching of chemicals from various plastic products depends upon various parameters like leaching condition, pH, water quality parameter, temperature and location. In this study concentration of chemicals in drinking water after leaching from bottles and in surface water as reported in literature are used directly. Concentrations reported in studies are directly used.

Estimation of Average Daily Dose: For drinking water

After obtaining the concentration, value of average daily dose (ADD)(mg/kg wt/d) is calculated using chemicals following formula [27].

$$\mathrm{ADD} = \frac{\mathrm{C_d} \times \mathrm{DI_d}}{\mathrm{BW}} \tag{1a}$$

C_d: contaminant level in drinking water (ng/L); DI_d: average daily intake of drinking water (L/d); BW: Body weight (kg)

Estimation of Average daily dose: For surface water (Swimming purpose)

$$\mathrm{ADD} = \frac{\mathrm{C_s} \times \mathrm{DI_s}}{\mathrm{BW}} \tag{1b}$$

C_s: contaminant level in drinking water; DI_s (ng/L): average daily intake while swimming in surface water (L/d); BW: Body weight (kg)

Table 3. Parameter values used for calculating ADD

Body weight	DI_d (Drinking water)	DI_s (Swimming)
60Kg[21]	2L/d[27]	0.1L/d[38]

2.3 Dose-response assessment

For individual compound— data from the US EPA IRIS has been obtained based on the toxicity studies conducted for, BPA and DEHP. RfD value of 5×10^{-2} mg/kg/day was obtained for exposure of humans to BPA[39]. The critical effect observed was reduced mean body weight. Similarly, RfD value for DEHP[40] was reported as 2×10^{-2} mg/kg/day and critical effect was increased relative liver weight. DEHP is also a possible human carcinogen having oral slope factor of 1.4×10^{-2} /mg/kg/day as classification — B2 that is , probable human carcinogen by IRIS[40]. In case of BPA, no adequate evidence is available on carcinogenicity.

For the case of mixture of chemicals, literature was reviewed to compile all available knowledge to see if RfD and/or PF can be determined.

2.4 Risk Characterization

Risk is estimated for hypothetical exposure of individual chemical and/or mixture of chemical through drinking and/or swimming activity.

2.4.1 Individual chemical:

For non-cancerous chemical, like BPA, hazard quotient (HQ) is calculated as

$$\mathrm{HQ} = \frac{\mathrm{ADD}}{\mathrm{RfD}} \tag{2}$$

If HQ is less than 1.0, there should be no significant risk or systemic toxicity. Ratios above 1.0 could represent a potential risk.

For cancerous chemicals, incremental life time risk of cancer (LCR) is calculated. In present study, DEHP is potential carcinogen while BPA does not show any evidence of carciogenicity.

$$\text{Incremental life time risk} = \mathrm{CDI} \times \mathrm{PF} \tag{3}$$

Where, chronic daily intake is given by:

$$\mathrm{CDI} = \frac{\mathrm{C} \times \mathrm{CR} \times \mathrm{EF} \times \mathrm{ED}}{\mathrm{BW} \times \mathrm{AT}} \tag{4}$$

PF is Potency Factor; CDI is chronic daily intake by ingestion (mg/kg day), CW is chemical concentration in water (mg/L), IR is ingestion rate (L/day), EF is exposure frequency (days/year), ED is exposure duration (years), BW is body weight (kg), AT is averaging time [27].

2.4.1 Mixture of chemicals: For mixture of chemicals, risk is estimated in terms of Hazard index which is defined as a "weighted sum of the exposure measures for the mixture component chemicals" [41]. There are two cases: involving interaction of chemicals and not involving interaction between chemicals.

1. When there is no interaction—Dose additivity case

If more than one chemical is present then sum of individual hazard quotient is known as hazard index. Toxicity and exposure data are required for calculation.

$$\mathrm{HI} = \sum_{j=1}^{n} \mathrm{HQj} \tag{5}$$

Where, HQ_j is hazard quotient for jth chemical obtained from Eq 2.

2. When interaction is observed between chemicals— Weight of evidence approach

In this method HQ is modified in the formula by multiplying it with some factor considering effect of mixture toxicity and interaction.

The interaction-based HI can be calculated as follows (US EPA method) [41]

$$HI_{int} = \sum_{i=1}^{n} (\mathrm{HQ_i} \times \sum_{j \neq i}^{n} \mathrm{f_{ij}}\, \mathrm{M_{ij}^{B_{ij}\theta_{ij}}}) \tag{6}$$

$$\mathbf{f_{ij}} = \frac{\mathbf{HQ_j}}{\mathbf{HI_{add}} - \mathbf{HQ_i}} \tag{7}$$

$$\boldsymbol{\theta_{ij}} = \frac{\left(\mathbf{HQ_i} \times \mathbf{HQ_j}\right)^{\mathbf{0.5}}}{(\mathbf{HQ_i} + \mathbf{HQ_j}) \times \mathbf{0.5}} \tag{8}$$

HI_{int} = HI modified by binary interactions data; HQ_i = hazard quotient for chemical i ; f_{ij} = toxic hazard of the jth chemical relative to the total hazard from all chemicals potentially interacting with chemical i (thus j cannot equal i); M_{ij} = interaction magnitude, the influence of chemical j on the toxicity of chemical I; B_{ij} = score for the strength of evidence that chemical j will influence the toxicity of chemical I; Θij = degree to which chemicals i and j are present in equitoxic amounts.

Value of Bij is obtained from Table 4.

Table 4. Classification and Default Weighting Factors For The Modified Weight of Evidence (USEPA, 2000)[41]

Category	Description	Direction	
		Greater than additive	Less than additive
I	The interaction has been shown to be relevant to human health effects and the direction of the interaction is unequivocal.	1	-1
II	The direction of the interaction has been demonstrated in vivo in an appropriate animal model, and the relevance to potential human health effects is likely.	0.75	-0.5
III	An interaction in a particular direction is plausible, but the evidence supporting the interaction and its relevance to human health effects is weak.	0.5	0
IV	The assumption of additivity has been demonstrated or must be accepted.	0	0

Considering interaction between BPA and DEHP, Eq 6 can be applied. Since there are two chemical interacting with each other, value of Fij=1. Value of B is obtained by assuming category II. It was selected since there was uncertainty due to lack of evidence. But some *in vivo* studies are available showing combined effect of both chemical on human[42],[43]. Mixture of plastic constituents like BPA and DEHP promote epigenetic transgenerational inheritance of adult onset disease: Obesity and reproductive disease[42]. Studies show that BPA and phthalate may induce neurobehavioral disturbances and disruption of social and parental behaviors[43]. HI interaction is calculated by assuming synergistic effect with Bij value of 0.75 and by assuming antagonistic effect with Bij value of -0.5. HI interaction is also calculated by assuming category of B as I including synergistic as well as antagonistic effect. For mixture of two chemical value of $B_{12}=B_{21}$.Value of M here is set as 5 according to US EPA[41].

The above used methodology gives HI for three scenarios: no interaction, interaction leading to synergistic effect and interaction leading to antagonistic effect. These values were compared to know variation of HI and to know uncertainty in risk estimate.

3. RESULTS AND DISCUSSIONS

3.1 Risk estimate for individual plastic constituents.

For calculating risk of individual components, concentration range is obtained from Table 1. Concentration of BPA from exposure of drinking bottled water range between 0.5-31ng/L and from surface water range between 8.24-21000ng/L. Concentration of DEHP from exposure of drinking bottled water is between 100-8780 ng/L and from surface water between 8000-320000ng/L. Using maximum concentration values, ADD and HQ are calculated as shown in Table 5. Lifetime incremental risk (LCR) is calculated for DEHP to show effect of carciogenicity.

Table 5. Calculated risk estimate values of hypothetic exposure of BPA and DEHP (no mixture toxicity)

Water type	Concentration (µg/L)	ADD(µg/kg wt/d) (Eq 1a & 1b)		
			HQ(Non-cancerous)	LCR(Cancerous)
Non-cancerous effects BPA (RfD=50 µg/kgwt/d)				
Drinking water	0.031	1.03×10^{-3}	2.06×10^{-5}	-
Surface water	21	0.035	7×10^{-4}	-
Effects due to DEHP (RfD=20 µg/kgwt/d; PF=1.4×10^{-2} /mg/kg/day)				
			HQ(Non-cancerous)	LCR(Cancerous)
Drinking water	8.780	0.293	0.0146	4.102×10^{-6}
Surface water	320	0.533	0.0267	7.462×10^{-6}

Hazard quotients were found to be below 1 indicating no chance of non-cancerous effect. LCR of DEHP was found to be greater than one in million (1 in 1000000) (Guideline value), hence there is risk of cancer. (US EPA)

3.2 Risk estimate for mixture of chemicals

Risk from exposure of human to chemical mixtures is evaluated in terms of hazard index as shown in Table 6. It was inferred from hazard index (For non-cancerous effect) value that there is no risk involved and water is safe. Table 7 represents calculation of hazard index for mixture of chemicals with interaction. Values of hazard index shows there is negligible risk from combined effect of mixture of chemical.

Table 6. Calculated risk estimate values of exposure to chemical mixture (Without interaction)

Reference (Data Source)	Exposure scenario	Concentration		DEHP (RfD=20µg/kg wt/d)		BPA (RfD=50µg/kgwt/d)		Hazard Index(Non-Cancerous)
		DEHP (µg/L)	BPA (µg/L)	ADD_1	HQ_1	ADD_2	HQ_2	
Casajuan and Lacorte (2003)	Ingestion of drinking water	0.134	0.01	0.004467	0.000223	0.005667	0.000113	0.000337
Amiridou and Voutsa, 2011	Ingestion of drinking water	0.580	0.170	0.019333	0.000967	0.000333	6.67×10^{-6}	0.000973
Fromme et al.(2001)	Ingestion during Swimming	97.8	0.41	0.163	0.00815	0.683333	0.013667	0.021817
Tran et al.(2015)	Ingestion during Swimming	1.7	0.79	0.002833	0.000142	1.316667	0.026333	0.026475

Table 7. Calculated Risk estimate of exposure of chemical mixture (With interaction) ($F_{12}=F_{21}=1$; $M_{12}=M_{21}=5$; Bij=Category I and Category II)

Data Source	Exposure Scenario	HQ_1	HQ_2	$\theta_{ij}=\theta_{12}=\theta_{21}$	$B_{ij}=B_{12}=B_{21}$ (Category II)		$HI_{int}=\sum_{i=1}^{n}(HQ_i \times \sum_{j\neq i}^{n} f_{ij} M_{ij}^{B_{ij}\theta_{ij}})$	
					S	A	Synergism	Antagonism
Casajuan and Lacorte (2003)	Ingestion of drinking water	0.000223	0.000113	0.94511	0.75	-0.5	0.001054	0.000157
Amiridou and Voutsa, 2011	Ingestion of drinking water	0.000967	6.67×10^{-6}	0.16495	0.75	-0.5	0.001188	0.000852
Fromme et al.(2001)	Ingestion during Swimming	0.00815	0.013667	0.96750	0.75	-0.5	0.070142	0.010015
Tran et al.(2015)	Ingestion during Swimming	0.000142	0.026333	0.14590	0.75	-0.5	0.031574	0.023542
Data Source	Exposure Scenario	HQ_1	HQ_2	$\theta_{ij}=\theta_{12}=\theta_{21}$	$B_{ij}=B_{12}=B_{21}$ (Category I)		$HI_{int}=\sum_{i=1}^{n}(HQ_i \times \sum_{j\neq i}^{n} f_{ij} M_{ij}^{B_{ij}\theta_{ij}})$	
					S	A	Synergism	Antagonism
Casajuan and Lacorte (2003)	Ingestion of drinking water	0.000223	0.000113	0.94511	1	-1	0.0015	7.34×10^{-5}
Amiridou and Voutsa, 2011	Ingestion of drinking water	0.000967	6.67×10^{-6}	0.16495	1	-1	0.0013	0.000746
Fromme et al.(2001)	Ingestion during Swimming	0.00815	0.013667	0.96750	1	-1	0.1035	0.0046
Tran et al.(2015)	Ingestion during Swimming	0.000142	0.026333	0.14590	1	-1	0.0335	0.0209
S- Synergism, A- Antagonism								

Hazard Index is calculated for three scenario (i) HI: Dose additivity (Without interaction); (ii) HI: With interaction (Synergism); (iii) With interaction (Antagonism). In all the above cases, value of HI was found to be less than 1, indicating no risk.

4. Summary and Conclusion

This study shows estimation of risk resulting from mixture of plastic-based EDC on human health using an example calculation. The above theory was represented with the help of example calculation. Various knowledge gaps were identified and corresponding suggestive actions were proposed in Table 8. These identified data gaps need to be filled by conducting more research in this direction so that exposure of population to polymeric compounds and chemicals in water from plastic waste can be estimated with more confidence and efforts for protecting them can be made. Points which are shaded represent top three knowledge gaps. If these data gaps are identified, then Eq 6 as given by US EPA can be applied for mixture of plastic constituents with maximum accuracy.

Table 8. Identified knowledge gap and suggested actions at various steps of risk assessment

Hazard Identification	**Suggested Actions**
1. Lack of Information about co-occurrence of plastic constituents.	Inventory of occurrence of plastic constituents in environment needs to be developed.
2. Combined toxicity information not available	Toxicology research needs to be carried out for mixture of plastic constituents dosing.
3. No methodology to identify mixtures	Monitoring of constituents simultaneously to determine chance of co-occurrence.
Exposure Assessment	
1. Aggregate effect of mixture through various routes of exposure.	More research needs to be done to understand combined effect from oral, dermal and inhalation route.
2. Concentration of BPA and DEHP simultaneously in drinking water and surface water is limited.	More laboratory and field monitoring data by collecting more samples and analyzing them.
3. Temporal variability is not taken into consideration while calculating concentration.	Kinetic models involving time as factor needs to be considered for calculating concentration.
4. Uncertainty exists in accuracy of exposure data.	Application of new technology to epidemiology[44]. Use of Biomarkers
Dose Response	
1. RfD value of mixture of plastic constituents is not available.	Modeling needs to be done to derive combined RfD formula; Create database to generate combined RfD value
2. Toxicological similarity between mixtures of constituents not available.	More study on toxicology.
3.Interaction type (Synergism and Antagonism)	More information to be obtained from dose-response studies; information on toxicity mechanisms; mode of action; *in vivo* and *in vitro* studies
Risk Characterization	
1.Interaction effect from cancerous and non-cancerous plastic constituents	Research on combine effect of cancerous and non-cancerous plastic constituents.
Weight of evidence factor(B) 1.Based on data made by group of experts 2. They are rough values and will change with more research on interaction of chemicals.[41] 3.Synergism and antagonism	Some mathematical basis needs to be developed for estimating this factor. More information on combined effect of plastic constituents on human.
Interaction magnitude(M) 1. Synergism and Antagonism interaction not considered.	More research on synergism and antagonism effect.

2. Generally value is taken as 5 but this does not have strong empirical background.[41]	Empirical equation needs to be developed.

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