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ORIGINAL ARTICLE

# Human Health Risk Assessment due to Solvent Exposure from Pharmaceutical Industrial Effluent: Deterministic and Probabilistic Approaches

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## Abstract

Treated effluents from a pharmaceutical industry were analysed using purge and trap coupled with gas chromatography-mass spectrophotometry to determine the presence of organic solvents. Solvents such as dichloromethane, chloroform, toluene, tetrahydrofuran and chlorobenzene were detected. A health risk assessment study using both the deterministic method and a probabilistic approach by Monte Carlo simulations were then carried out on children, adults and pregnant women considering oral ingestion, dermal contact and fish intake as the exposure routes. Among the various categories of receptors considered, the results obtained by both methods revealed that children are more sensitive followed by pregnant women, since their total hazard index ($HI_{total\ risk}$) exceeded the safe exposure limit for non-carcinogens. It is also evidenced that oral and dermal contact are the crucial routes of exposure among children, adults and pregnant women. The fish intake had the minimal impact on all receptors, which might be due to the lesser affinity of these solvents to sorb onto fish tissues. Cancer risk because of dichloromethane and chloroform exposure was found to be negligible ($2.8\times10^{-8}$ for children, $1.3\times10^{-7}$ for adults, $3.9\times10^{-7}$ for pregnant women) since the computed risk was well below the acceptable range ($10^{-4}$ - $10^{-6}$). The total non-carcinogenic risk calculated from the probabilistic approach exceeded the deterministic approach by 1.9 times, 1.02 times, 1.8 times for children, adults and pregnant women, respectively. This might be due to incorporating lower values among the possible range for the parameters involved during deterministic risk assessment.

**Keywords** Risk assessment · Monte Carlo simulation · Hazard Index · Solvents · Pharmaceutical industry

**Article highlights**

- Carcinogenic and non-carcinogenic solvents were found in pharmaceutical effluent
- Health risk assessment on children, adults and pregnant women were studied
- Non-carcinogenic risks were likely to occur in all receptors as Hazard Index was >1
- Oral ingestion and dermal contact were found to be the critical exposure routes
- No health concerns due to carcinogenic solvents were observed

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## 1 Introduction

Solvents play a significant role in the manufacturing and synthesis operations of pharmaceutical industry to develop different medications such as tablets, syrups, and injectables. As the quantity of solvents required for production is very high compared to other raw materials, their risk to the ecosystem and human health is of great concern. Many reports have pointed out the consequences caused either due to the ingestion, inhalation, or physical contact with solvents (Lee et al. 2002; Yang et al. 2007; Fan et al. 2009; Guyton et al. 2014). Solvents cause liver toxicity, asthma, genetic disorders, and skin irritations in humans and also affect the cell membrane and lung capacity (Rees et al. 1993; Ukai et al. 1994; Vandenplas et al. 2013; Carder et al. 2019). The magnitude of these impacts varies depending on their toxicity, persistency and bioaccumulative characteristics (Wong et al. 2012; Sorengard et al. 2019; Rudel et al. 2020). Researchers have concentrated their studies on the detection, quantification, removal and recovery of solvents from water or wastewater (Agrawal et al. 2011; Ramirez et al. 2011; Modla and Lang 2012; García et al. 2013; Girish and Murty 2015; Pitiriciu and Tansel 2021).

Even though regulatory bodies have mandated the industries to treat their effluents before discharge, various research studies have still identified the presence of these contaminants in the aquatic environment. This is mainly because most of the existing treatment plants are unequipped to remove these toxic pollutants (LuoY et al. 2014; Blum et al. 2017; Gago-Ferrero et al. 2017; Noutsopoulos et al. 2020).

Though several studies have addressed the impacts of solvents, no significant research work has focused on the possible adverse effects on health due to the exposure of solvents to various receptors when present in trace amounts in water bodies. Also, maximum contaminant levels for most solvents are not defined in any drinking water standards. So, there is an ambiguity among industries to define the limit of residual solvent concentration in their treated effluents. Even though a trace amount of residual solvent concentration is present in water bodies, the impact of these solvents on the receptors can be alarming.

Human health risk assessment plays a significant role in quantifying the risk from chemical exposure, thereby defining permissible limits for contact and any remedial strategies for the contaminated site. European Union Directive 92/32/EC and European Commission Council Regulation 793/93 have mandated a risk assessment for new and existing chemicals, respectively. Since 1970, the US EPA has practised risk assessment studies on pesticides, organic solvents and other chemicals (Kanwar 2018). Two approaches are widely used for health risk assessment: the deterministic approach and the probabilistic approach. The probabilistic risk assessment approach is generally preferred over the deterministic approach as the latter involves a high degree of variability since it considers constant values for the parameters of concern (Bruce et al. 2007; Kaur et al. 2020).

Till date, many researchers have carried out human health risk assessments in diversified fields such as heavy metals (Alidadi et al. 2019; Hu et al. 2019; Ghosh et al. 2020; Guleria and Chakma 2021; Orosun 2021; Shokoohi et al. 2021), polyaromatic hydrocarbons (Bruce et al. 2007; Wu et al. 2011; Rajasekhar et al. 2018; Shi et al. 2020; Ofori et al. 2021), fluorides and nitrates in groundwater (Narsimha and Sudarshan 2017; Kaur et al. 2020; Rishi et al. 2020; Singh et al. 2020), occupational exposure to volatile organic solvents (Akdeniz et al. 2013; Banton et al. 2019), groundwater quality (Raju and Singh 2017), inhalation risk in workers (Liao et al. 2010; Wang et al. 2013a) and pharmaceuticals (Kumar et al. 2010; Srinivasan et al. 2021) considering infants, children and adults as receptors. Also, many researchers have approached the risk assessment studies using

uncertainty-based techniques (Bakhtavar et al. 2021; Karunathilake et al. 2020). But studies on the health risk of solvent exposure on pregnant women as potential receptors have not been carried out.

Thus, the present study on human health risk assessment due to solvent exposure from pharmaceutical industrial effluent is focused on: (1) determining the presence of various organic solvents in the treated effluent from a pharmaceutical industry; (2) estimating human health risk due to residual solvent in water bodies by both the deterministic approach and the probabilistic approach; (3) identifying the most sensitive receptors among children, adult and pregnant women when exposed to a solvent contaminated surface water; and (4) determining the critical exposure pathway among the various possible exposure routes. The outcome shall provide a comprehensive outlook on the human health risk due to the presence of solvents in water, which can help in adopting managerial decisions for abating pollution.

## 2 Materials and Methods

In a risk assessment study, various stages are involved, namely, hazard identification, exposure assessment, toxicity analysis and risk quantification (US EPA 2004). The hazard identification stage detects the contaminant of concern in the study area. Exposure assessment identifies the mode of entry of contaminants into human body through: (a) oral intake of contaminated drinking water; (b) through dermal absorption; (c) inhalation of volatile or semi-volatile contaminant vapours; and (d) fish intake (US EPA 1989; IPCS 2010). Toxicity assessment analyses the body's response to either alter or retain or eliminate the fraction of a contaminant entering the body. The response can either be acute, subchronic, or chronic, depending on the exposure duration and contaminant concentration. Risk quantification is the final stage in which carcinogenic and non-carcinogenic risks are calculated from all possible exposure pathways (US EPA 2004). Fig. 1 shows the framework of human health risk assessment.

### 2.1 Sample Collection and Analysis

Samples of effluent from the outlet of the wastewater treatment plant of a pharmaceutical industry in Vishakhapatnam city, Andhra Pradesh State, India were collected and analysed to examine the presence of various volatile organic components. Effluent along with its duplicate were collected in 1-L amber bottles up to their brim. The bottles were rinsed with methanol and Milli-Q water prior to the sample collection. The collected samples were stored at 4 °C till analysis. Purge and trap (PT) coupled with gas chromatography-mass spectrophotometry (GCMS) operated in splitless injection mode with a column temperature of 250 °C and carrier helium gas flow rate of 1 mL $min^{-1}$ was used to detect the volatile compounds present in the effluent. The samples were analysed as per US EPA method 5030C (US EPA 2003). The details of the operating conditions for estimating the samples are listed in Table 1. The compounds were detected based on the retention time (RT in min) and mass spectra obtained. PT purges the volatiles from the aqueous media to the gaseous phase, and then, they are trapped onto the adsorbent, usually Tenax, silica gel, activated charcoal, or carbon molecular sieve (Sparkman et al. 2011). The trap is then heated to desorb the volatiles and then injected to GCMS for detailed analysis. This helps in analysing the compounds with a lower boiling point.

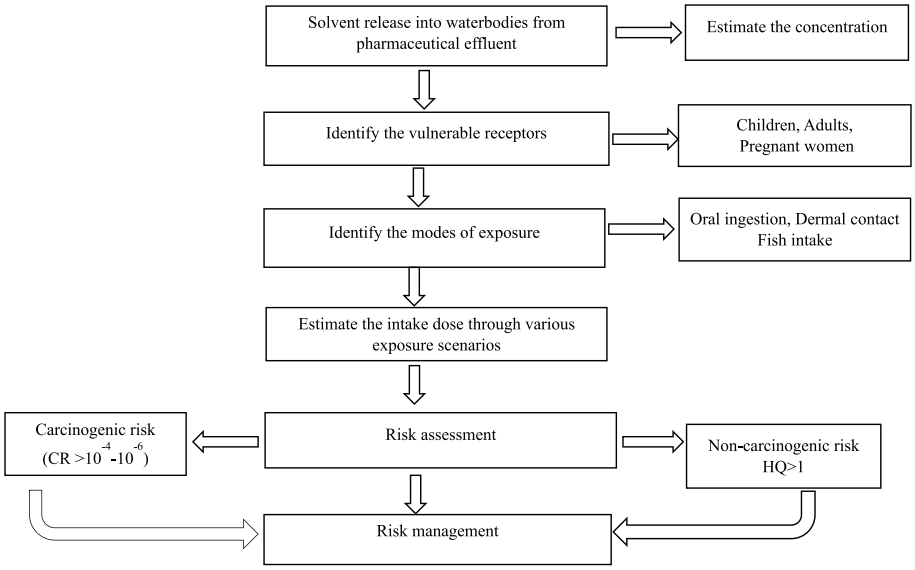



**Fig. 1** Framework of human health risk assessment

**Table 1** Operating conditions used in purge and trap analysis

| Parameter | Value |
|---|---|
| Sample volume | 5 mL |
| Valve oven temperature | 140 °C |
| Transfer line temperature | 140 °C |
| Sample Mount temperature | 90 °C |
| Sample vial temperature | 20 °C |
| Standby flow | 10 mL/min |
| Sweep sample time | 0.25 min |
| Sweep sample flow | 100 mL/min |
| Purge time | 9 min |
| Purge flow | 40 mL/min |
| Purge temperature | 20 °C |
| Dry purge flow | 100 mL/min |
| Desorb preheat temperature | 245 °C |
| Desorb time | 2 min |
| Desorb temperature | 250 °C |
| Bake time | 2 min |
| Bake flow | 200 mL/min |
| Bake temperature | 280 °C |
| Injection time | 1 min |
| Injection temperature | 180 °C |

## 2.2 Human Health Risk Assessment

The risk assessment due to solvent exposure is determined on the exposed population classified as children, adults and also on pregnant women, based on the models provided by the US EPA (2000, 2001, 2004). Since the waste solvents enter the water bodies, the main exposure routes are ingestion (drinking water, accidental intake during bathing), dermal contact (bathing, swimming, fishing etc.) and fish intake. Though the concentration of solvents present in water bodies is in trace amount, their impact on the receptors can be alarming, particularly in children and pregnant women. Till now, very few studies have addressed pregnant women as potential receptors. In humans, the gestation period is 40 weeks or 280 days, which is considered as exposure frequency in pregnant women. Exposure duration refers to the duration over which the exposure towards the contaminant is assessed, and in case of pregnant women, it is examined for a duration of 10 months (0.83 years).

Table 2 provides the parametric values used in calculating the risk via the deterministic approach. The equations that are used to calculate the dose due to various exposure routes to receptors are briefly explained as follows: Daily intake (DI) due to ingestion is calculated based on the following equation (US EPA 2001):

$$\mathrm{DIoral} = \frac{C_i \times IR_1 \times ED \times EF \times RBA}{BW \times AT} \tag{1}$$

where $C_i$ = solvent concentration (mg/L) in water, $IR_1$ = ingestion rate (L/day), ED = exposure duration (years), EF = exposure frequency (days/year), BW = body weight (kg), AT = averaging time (days), RBA= relative bioavailability.

Relative bioavailability refers to the fraction of chemical dose that finally reaches the human body to trigger a response. It is an important parameter in risk assessment to identify the potential hazard (Orosun 2021). As per US EPA (1989), bioavailability can assume the value of 1 in oral ingestion considering the bioavailability of solvent to be the same as in water medium.

Daily intake can also occur through dermal contact either by skin absorption during bathing or swimming. For organic compounds, the dermal risk is calculated by the

**Table 2** Values of exposure parameters used in deterministic approach

| Parameters | Units | Children | Adults | Pregnant women | Reference |
|---|---|---|---|---|---|
| Body weight | kg | 15 | 70 | 70.4 | Jimenez-Oyola et al. (2021); Ershow et al. (1991); Santacruz et al. (2010) |
| Injection rate | L/day | 0.09 | 0.053 | 1.1 | |
| Fish intake | g/day | 0.200 | 0.100 | 12.7 | Kortei et al. (2020) ; Lando et al. (2012) |
| Exposure Frequency | days/year | 350 | 350 | 280 | US EPA (2001) Jukic et al. (2013) |
| Exposure Duration | Years | 6 | 30 | 0.83 | Jimenez-Oyola et al. (2021); Collier (2007) |
| Skin surface area | $cm^2$ | 7280 | 23000 | 16200 | |
| Event frequency | events/day | 1 | 1 | 1 | US EPA (2004) |
| Fraction of skin in contact with water | - | 1 | 1 | 1 | US EPA (2004) |
| Event duration | h/event | 0.33 | 0.25 | 0.25 | US EPA (2011) |

following equations as given by the US EPA (2004) by taking into consideration the event duration, lagtime per event and the fraction of water absorbed onto the skin:

$$DI_{dermal} = \frac{DA_{event} \times EV \times ED \times EF \times SA}{BW \times AT} \quad (2)$$

where

$$DA_{event} = 2 \times FA \times K_p \times C_i \times \sqrt{\left(\frac{6 \times \tau_{event} \times t_{event}}{\pi}\right)}, \text{since } t_{event} < t* \quad (3)$$

The time required to attain steady state is:

$$t* = 2.4 \times t_{event} \quad (4)$$

where $K_p$ = skin permeation coefficient (cm/h), FA = fraction of skin in contact with water (unitless), SA = area of the exposed skin ($cm^2$), EV = frequency of the event (events/day),

$\tau_{event}$ = lagtime per event (h/event), $t_{event}$ = event duration (h), t*= time to reach steady-state (h). The chances are there for these solvents to sorb onto fish tissues which mainly depend on the properties of the chemicals such as water solubility as well as the bioconcentration factor. The daily intake due to fish consumption can be calculated as (US EPA 2000):

$$DI_{fish} = \frac{C_i \times BCF \times IR_2 \times ED \times EF}{BW \times AT} \quad (5)$$

where BCF = bioconcentration factor (L/kg), $IR_2$ = fish intake rate (kg/day), AT = averaging time (days), which in case of non-carcinogens, are averaged over its exposure duration (ED) and for carcinogens it is averaged over lifetime:

$$AT_{non\ carcinogens} = ED \times 365 \quad (6)$$

$$AT_{carcinogens} = 70 \text{ years} = 70 \times 365 = 25550 \text{ days} \quad (7)$$

The associated risk is calculated by multiplying the estimated daily intake with cancer slope factor (CSF) for carcinogens, whereas for non-carcinogenic solvents, the reference dose (RfD) is taken into account for computing the risk. The reference dosage and cancer slope factor, which are contaminant and exposure path specific, are obtained from the US EPA's Integrated Risk Information System (IRIS 2019) and Risk Assessment Information System (RAIS 2019) database.

The solvents for which the associated skin absorption reference dose is not available from the database, it is derived from their oral reference dose based on the Eq. (8) as given by Fallahzadeh et al. (2018):

$$RfD_{dermal} = RfD_{oral} \times ABS_{gi} \quad (8)$$

where $ABS_{gi}$ = intestinal absorption factor.

Non-carcinogenic risk, referred to as hazard index (HI) and carcinogenic risk (CR) are calculated using the following Eqs. (9) and (10), respectively, for each exposure pathway (US EPA 1989). HI estimates the total possible non-carcinogenic risk through different exposure pathways due to multiple solvents. When HI is greater than 1, it indicates the

possibility of non-carcinogenic risk, and when HI is less than 1, it shows no risk due to chemicals on receptors (Pirsaheb et al. 2021; Guo et al. 2019; Guerra et al. 2012; US EPA 2000):

$$HI = DI/RfD \tag{9}$$

$$CR = DI \times CSF \tag{10}$$

Total risk for receptors from all the exposure routes can be determined by:

$$HI_T = HI_{oral} + HI_{dermal} + HI_{fish\ intake} \tag{11}$$

$$CR_T = CR_{oral} + CR_{dermal} + CR_{fish\ intake} \tag{12}$$

where $HI_T$ and $CR_T$ refer to the total hazard index and total cancer risk, respectively, due to solvent exposure.

The EPA guidelines have demarcated the acceptable range of $CR_T$ within $10^{-4}$ to $10^{-6}$ excess lifetime cancer risk and for non-carcinogens, the acceptable $HI_T$ should be below 1 (Guerra et al. 2012; US EPA 2000).

### 2.3 Uncertainty Analysis Using Probabilistic Approach

The point approach (deterministic method) involves uncertainty since constant values are taken for the parameters during risk assessment which could be the higher values among the possible range (Kaur et al. 2020). In the probabilistic approach of risk assessment, considering the variability involved in the parameters of interest, the parameters are analysed using the best fit distribution, with all the possible values for the exposure parameters by Monte Carlo simulations with 10000 iterations using MATLAB 2020. The input variables vary during each iteration and a new value is assigned so as to find the risk in each subpopulation, thus incorporating elements of randomness during the analysis (Clemens 1996). The input variables used in the study are shown in Table 3. In pregnant women, the minimum gestation period is taken from 29 weeks and five days to a maximum gestation period of 40 weeks and four days (Jukic et al. 2013).

## 3 Results and Discussion

### 3.1 Solvent Detection from Wastewater

Solvents identified through purge and trap coupled with GCMS are the dichloromethane (DCM), chloroform, toluene, tetrahydrofuran and chlorobenzene. Among these solvents, dichloromethane and chloroform are classified as likely to be carcinogenic by the US EPA (2005), while the other solvents are non-carcinogens as per the International Agency for Research on Cancer (IARC). Permissible limits for these solvents, as reported by WHO (2017) drinking water standards, are for dichloromethane 0.02 mg/L, for chloroform 0.3 mg/L, and for toluene 0.7 mg/L. However, maximum contaminant levels for tetrahydrofuran and chlorobenzene are not provided in drinking water standards. The presence of solvents in water bodies has also been reported by the Changing Markets Foundation

**Table 3** Parameters used for the probabilistic risk assessment

| Parameter | Units | Distribution | Children | Adults | Pregnant women | Reference |
|---|---|---|---|---|---|---|
| Body weight | kg | Normal | 30.25 ± 19.27 | 79.1 ± 1.652 | 67±12 | US EPA (2011); Caetano et al. (2019) |
| Injection rate | L/day | Normal | 0.255 ± 0.057 | 0.859 ± 0.079 | 2.076±0.743 | US EPA (2011); Ershow et al. (1991) |
| Fish intake | g/kg day | Normal | 0.17 ± 0.15 | 0.17 ± 0.03 | 0.14±0.05 | US EPA (2011); Silver et al. (2007) |
| Exposure frequency | days/year | Triangular | Min: 180<br>Mode: 345<br>Max: 365 | Min: 180<br>Mode: 345<br>Max: 365 | Min: 208<br>Mode: 273<br>Max: 284 | Fallahzadeh et al. (2018); Guleria and Chakma (2021); Jukic et al. (2013) |
| Exposure Duration | years | Uniform | 0, 5 | 0, 50 | 0, 50 | US EPA (2011); Rajasekhar et al. (2018) |
| Skin surface area | $cm^2$ | Normal | 10100 ± 4300 | 19360 ± 840 | 18000 ± 1020 | US EPA (2011) |
| Event frequency | events/day | - | 1 | 1 | 1 | US EPA (2004); Zhang et al. (2019) |
| Fraction of skin in contact with water | - | Uniform | Min: 0.4<br>Max: 0.9 | Min: 0.4<br>Max: 0.9 | Min: 0.4<br>Max: 0.9 | Fallahzadeh et al. (2018) |
| Event duration | hr | - | 0.33 | 0.25 | 0.25 | US EPA (2004); Guleria and Chakma (2021) |

Note: Normal (mean ± standard deviation)

**Table 4** Concentration of solvents in surface water

| Solvents | Concentration (µg/L) |
|---|---|
| Dichloromethane | 874 |
| Chloroform | 324 |
| Toluene | 32300 |
| Tetrahydrofuran | 525 |
| Chlorobenzene | 1780 |

Source: Changing Markets Foundation report (2018)

(2018). Table 4 shows the concentration of solvents in water. The properties of the solvents and their reference doses are listed in Table 5. Throughout this paper, the concentration reported by the Changing Markets Foundation (2018) is taken for the risk assessment.

### 3.2 Hazard Identification

The risk assessment of both carcinogenic and non-carcinogenic solvents was examined deterministically and probabilistically to study their health impacts when the solvents were exposed through oral, dermal and fish uptake. These are discussed in later sessions with their intake in mg/kg day.

#### 3.2.1 Deterministic Approach

Carcinogenic as well as non-carcinogenic risk assessment due to solvent exposure on human health was estimated by the deterministic method, and the risk associated with each exposure pathway is shown in Table 6. The risk of developing non-carcinogenic impacts on health in children for a period of 6 years due to ingestion of water was found to be 2.84 and 10.8 by dermal contact, whereas the risk is negligible due to fish intake. Both oral and dermal risk exceeds the threshold value of 1 for the hazard index defined by US EPA (2000). Children have been found to be more susceptible to the risk, with the critical route of exposure being oral ingestion and dermal contact. Oral ingestion is the crucial route of exposure among pregnant women since their ingestion rate during pregnancy is higher to meet the growing baby's demand. The risk of developing cancer in children, adults and pregnant women through all the exposure routes was found to be within the acceptable range of $10^{-4}$ to $10^{-6}$, which indicated that carcinogenic solvents would not cause any significant health impact.

#### 3.2.2 Probabilistic Approach

The assessment was carried out for three population clusters: children, adults and pregnant women taking into account all the demographic variability using Monte Carlo simulations. Monte Carlo simulation is an iterative procedure where input variables vary during each iteration. Here the input parameters were provided as distributions and the output was presented as distribution of risk. Probability distributions are a more accurate way of explaining uncertainty in variables during a risk analysis (Maxwell et al. 2021; Orosun et al. 2020). The percentile values obtained through the probabilistic approach which pointed

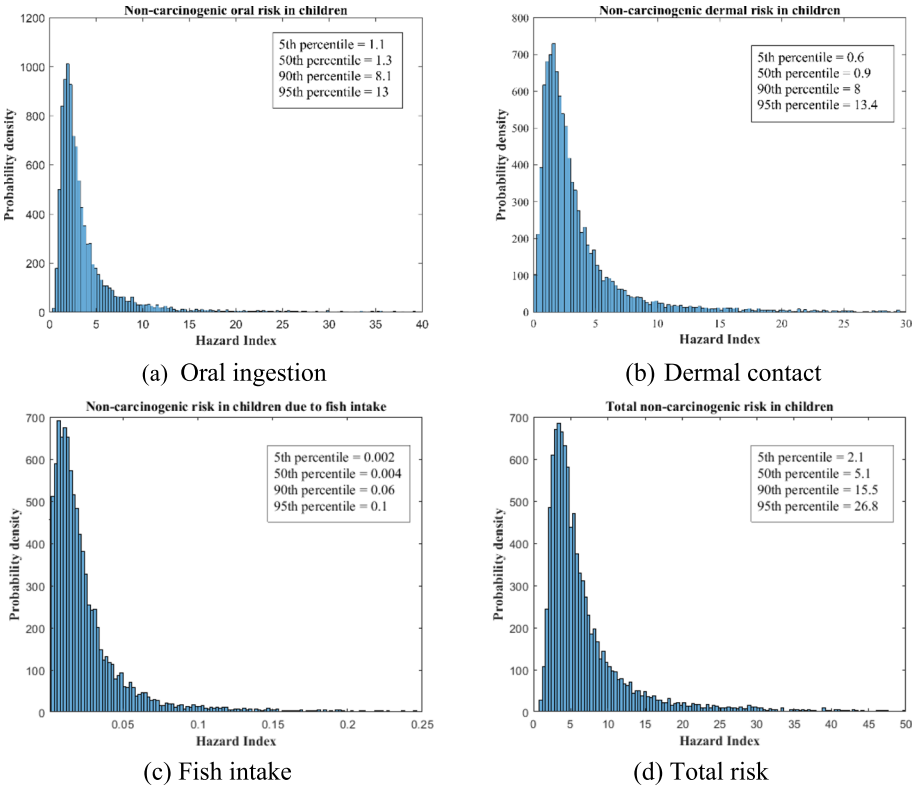
**Table 5** Solvent specific characteristics

| Solvents | Skin permeability coefficient ($K_p$) (cm/h) | Fish Bioconcentration Factor (L/kg) | Log Octanol Water Partition Coefficient (log $K_{ow}$) | Water Solubility at 25°C (mg/L) | Lag time per event (hr/event) $\tau_{event}$ | t* (hr) | Oral Rfd (mg/kg-day) | Dermal Rfd | Oral CSF $(mg/kg\text{-}day)^{-1}$ | Dermal CSF $(mg/kg\text{-}day)^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Dichloromethane | 0.0035 | 23.1 | 1.25 | $1.3\times10^4$ | 0.314 | 0.753 | - | - | 0.002 | 0.002 |
| Chloroform | 0.0068 | 13.0 | 1.97 | $7.9\times10^3$ | 0.489 | 1.175 | - | - | 0.031 | 0.031 |
| Toluene | 0.0311 | 8.32 | 2.73 | $5.3\times10^2$ | 0.344 | 0.827 | 0.08 | 0.064 | - | - |
| Tetrahydrofuran | 0.0012 | 3.16 | 0.46 | $1.0\times10^6$ | 0.266 | 0.639 | 0.9 | 0.9 | - | - |
| Chlorobenzene | 0.0282 | 17.8 | 2.84 | $4.0\times10^2$ | 0.448 | 1.076 | 0.02 | 0.0062 | - | - |

Source: RAIS, IRIS

**Table 6** Assessed values of risk on children, adults and pregnant women due to solvent exposure by deterministic approach

| Receptors | Oral risk | Dermal risk | Risk due to fish intake | Total risk |
|---|---|---|---|---|
| Hazard index for non-carcinogenic risk assessment | | | | |
| Children | 2.84 | 10.8 | 0.06 | 13.7 |
| Adult | 0.36 | 6.4 | $6.8\times10^{-3}$ | 6.8 |
| Pregnant women | 5.91 | 3.57 | 0.68 | 10.16 |
| Carcinogenic risk assessment | | | | |
| Children | $5.81\times10^{-6}$ | $3.26\times10^{-6}$ | $1.9\times10^{-7}$ | $9.3\times10^{-6}$ |
| Adult | $7.34\times10^{-7}$ | $1.92\times10^{-6}$ | $2\times10^{-8}$ | $2.7\times10^{-6}$ |
| Pregnant women | $1.7\times10^{-6}$ | $1.5\times10^{-7}$ | $2.8\times10^{-7}$ | $2.1\times10^{-6}$ |




(a) Oral ingestion (b) Dermal contact

(c) Fish intake (d) Total risk

**Fig. 2** Non-carcinogenic risk assessment in children due to **a** Oral ingestion, **b** dermal contact, **c** Fish intake, and **d** Total risk

from a minimum to an extreme range of scenarios where the 5$^{th}$ percentile represents minimum or least risk scenario and the 95$^{th}$ percentile is the worst or extreme risk scenario.

**Non-carcinogenic Risk Assessment** The probability distribution of various exposure routes for non-carcinogenic solvents is shown in Figs. 2, 3 and 4, along with their percentile values (5$^{th}$, 50$^{th}$, 90$^{th}$, 95$^{th}$).

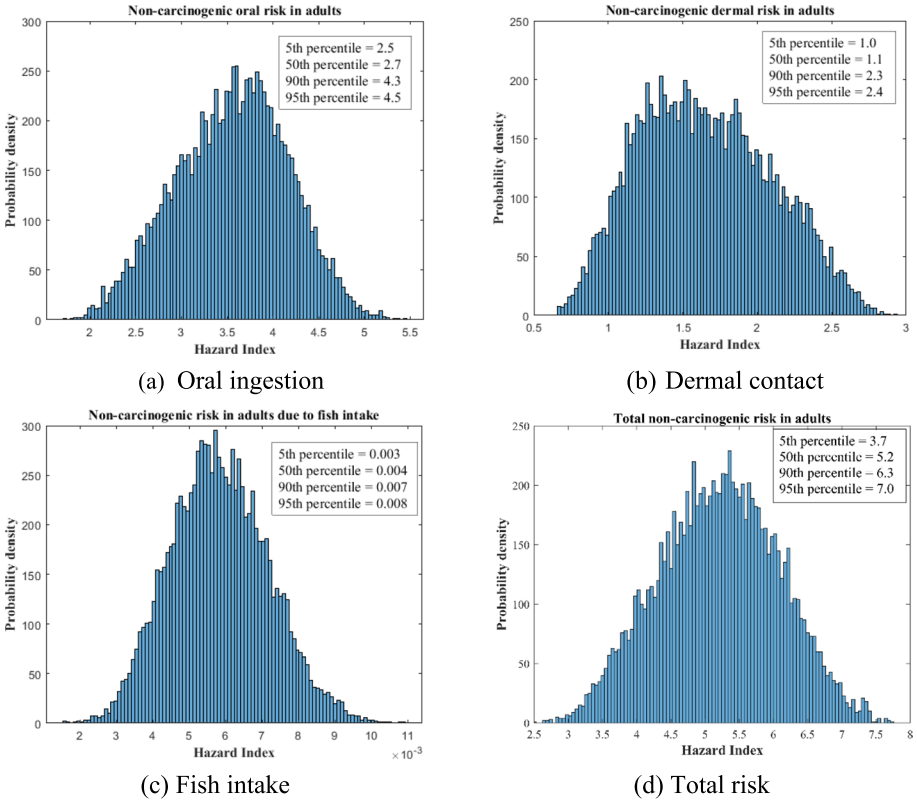



**Fig. 3** Non-carcinogenic risk assessment in adults due to **a** Oral ingestion, **b** Dermal contact, **c** Fish intake, and **d** Total risk

It was found out that the 95$^{th}$ percentile values for children and adults were 13 and 4.5 for oral ingestion, 13.4 and 2.4 through dermal contact and 0.1 and 0.008 due to fish intake. In pregnant women, 95$^{th}$ percentile values were found to be 16.0, 2.5 and 0.009 due to oral ingestion, dermal contact and fish intake, respectively. Also, the 5$^{th}$ percentile values for non-carcinogenic dermal risk in children and pregnant women were within the safe limit (HI<1), which indicates that 5 percent of the population exposed would not develop any risk from exposure to the solvents. 95$^{th}$ percentile value for total risk in children was found to be 26.8. Total non-carcinogenic risk in children exceeded the total risk in adults by 3.8 times and in pregnant women by 1.5 times. Children were more at risk to these solvents, which might be due to their higher metabolic rate and absorption capacities (Guo et al. 2019). The variation in their physical as well as metabolic features can influence the exposure; for instance, a higher body surface to body weight ratio, higher breathing rate, moderately higher intake of water and calories compared to adults. The Absorption, Distribution, Metabolism and Excretion (ADME) features can also vary from adults to children due to increased dermal permeability, higher digestive pH, gastric enzymes, immune response, alterations in metabolizing enzymes and differences in toxicokinetics and toxicodynamics (Bearer 1995; Chance and Harmsen 1998; Wolterink et al. 2002; Felter et al. 2015; Narciso et al. 2017). Among the three exposure routes considered, dermal contact has a significant

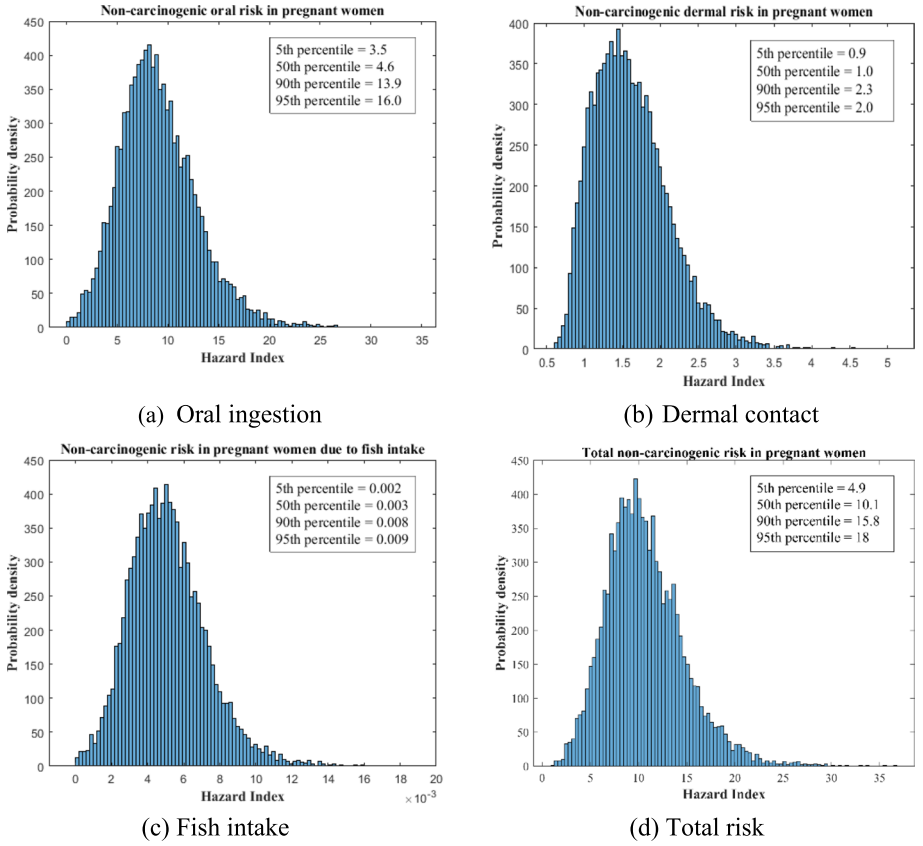


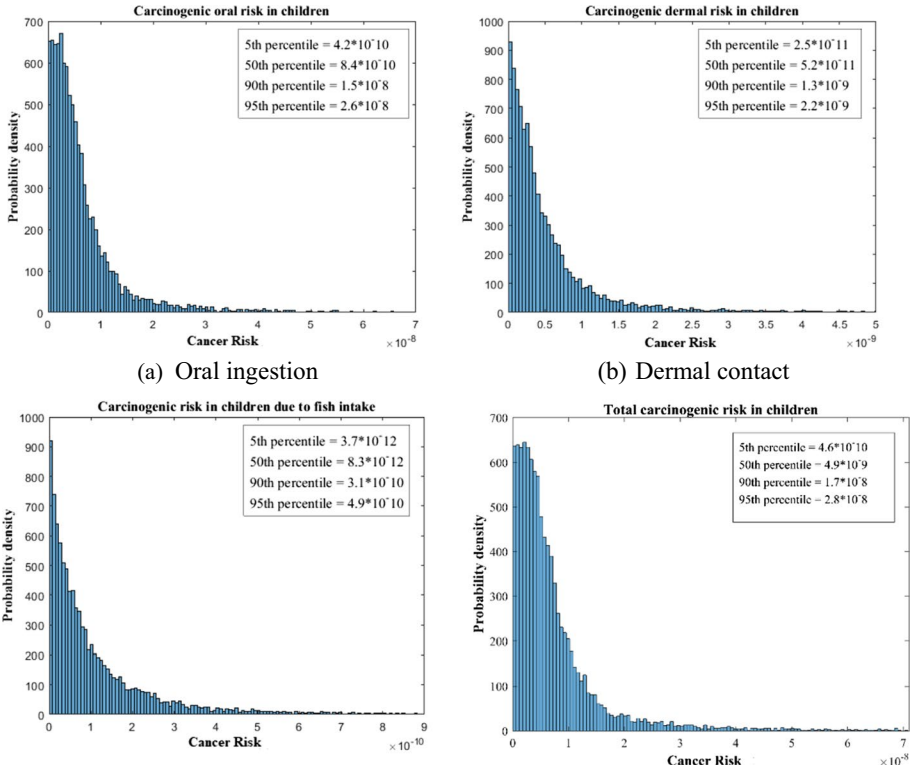

**Fig. 4** Non-carcinogenic risk assessment in pregnant women due to **a** Oral ingestion, **b** Dermal contact, **c** Fish intake, and **d** Total risk

effect on all receptors. Factors such as skin surface area, the fraction of skin exposed, and duration of contact were taken into account during the assessment, which can either control or permit absorption or penetration of the contaminants through the outer layer known as the stratum corneum to the epidermis, dermis, and finally, into the bloodstream. Studies have shown that organic solvents can alter the protein structure of the outer layer, thereby enhancing the permeation through the skin (Trommer and Neubert 2006), which might be the reason for the dermal exposure to be the critical pathway. In pregnant women, oral ingestion is found to cause adverse impacts. This is because of the increased oral intake of water for the foetal development and maternal health. Pregnant women have a different dietetic pattern due to which they tend to have higher water intake and food to meet the nutritional requirement and avoid any adverse pregnancy consequences (Lundqvist et al. 2014; Zhou et al. 2019). Higher water intake in pregnant women helps balance the amniotic fluid, prevent dehydration, enhance milk production and foetal development (Ndikom et al. 2014; Zhou et al. 2019). When compared to other modes of exposure, fish intake was found to have no impact on population since the HI is within the safe limit (HI<1). This can be explained by the least tendency of these solvents to sorb onto fish tissues, which is indicated by the bioconcentration factor, which in turn is related to the solubility of a chemical

and its water partition coefficient ($K_{ow}$). The chemicals with higher $K_{ow}$ are hydrophobic and partition to lipids or fatty tissues from water, which means they tend to bioconcentrate in aquatic tissues (Gestel et al. 1985; Mackay et al. 2015). Table 5 lists the $K_{ow}$ and BCF values for the solvents considered in this study. The solvents are more hydrophilic, which is supported by the findings of Howard and Muir (2013), in which they discussed that the bioaccumulative chemicals have their log $K_{ow}$ values greater than 3. Also, since these solvents are hydrophilic, the oral ingestion is found to have considerable health risks on all receptors.

The observations from this study are in agreement with similar risk assessment studies. Children are found to be more sensitive which is consistent with the studies by Jimenez-Oyola et al. (2021), Kaur et al. (2020), Guissouma et al. (2017) and Zhang et al. (2017). In the studies conducted by Rajasekhar et al. (2018), Guo et al. (2019) and Fallahzadeh et al. (2018) oral ingestion and dermal contact were found to be the critical routes of exposure, which is in accordance with the present study.

**Carcinogenic Risk Assessment** The probability distribution of various exposure routes for carcinogenic solvents is shown in Figs. 5, 6 and 7 along with their percentile values for children, adults and pregnant women, respectively. The 95$^{th}$ percentile values of all




(a) Oral ingestion (b) Dermal contact

(c) Fish intake (d) Total risk

**Fig. 5** Carcinogenic risk assessment in children due to **a** Oral ingestion, **b** Dermal contact, **c** Fish intake, and **d** Total risk

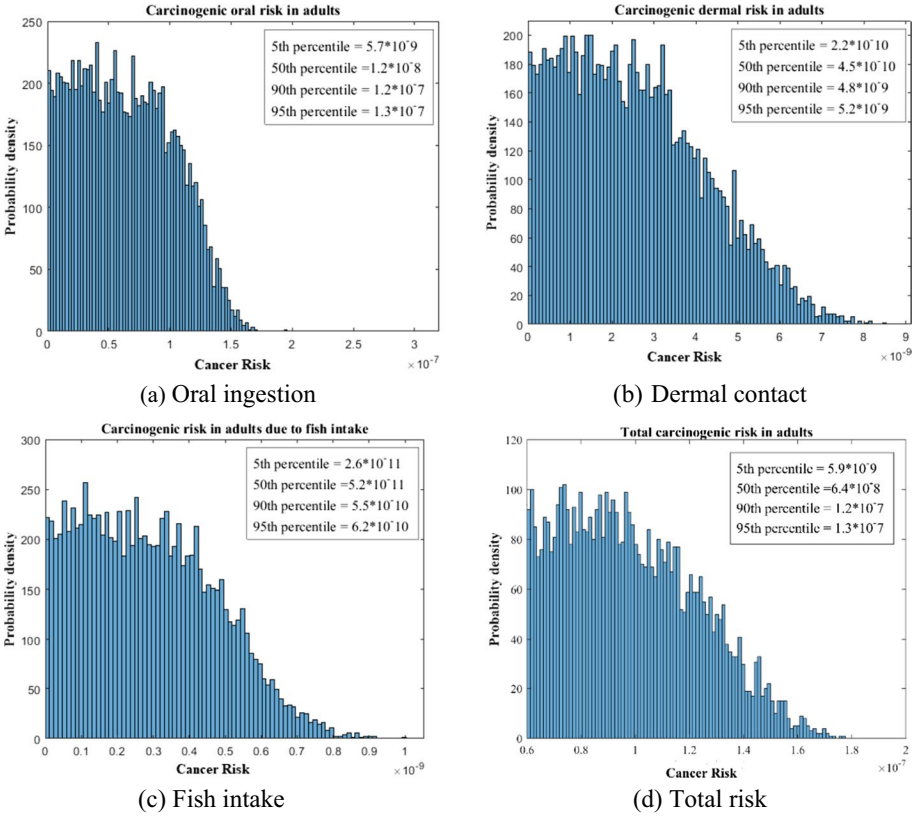



**Fig. 6** Carcinogenic risk assessment in adults due to **a** Oral ingestion, **b** Dermal contact, **c** Fish intake, and **d** Total risk

exposure routes were found to be in the safe exposure limit ($10^{-4}$ - $10^{-6}$), which means the exposed population has no cancer risk through any of the media of exposure. Similar results were obtained through the deterministic method for carcinogenic risk assessment.

## 4 Conclusions

The analysis of the treated effluent from the pharmaceutical industry showed the presence of both carcinogenic and non-carcinogenic solvents. In this study, deterministic and probabilistic risk assessment studies were carried out on children, adults, and pregnant women to quantify the risk from different exposure pathways. The total non-carcinogenic risk determined through the probabilistic method exceeded the deterministic approach in all receptors. This might be due to incorporating lower values among the possible range for the parameters involved during deterministic risk assessment. Children were found to be the most vulnerable to solvent exposure, followed by pregnant women and adults, which could be due to the variation in their metabolic characteristics. The critical exposure routes in the non-carcinogenic assessment were dermal contact and oral ingestion in children, adults and

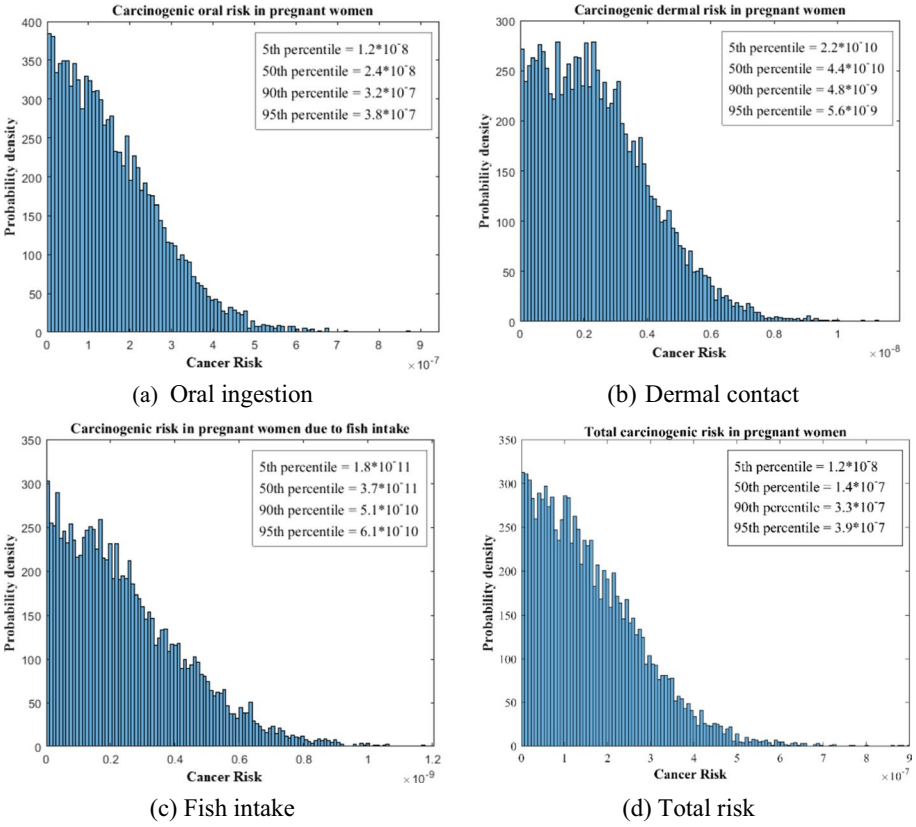



**Fig. 7** Carcinogenic risk assessment in pregnant women due to **a** Oral ingestion, **b** Dermal contact, **c** Fish intake, **d** Total risk

pregnant women. Fish intake showed to have a negligible impact on human health. Cancer risk due to solvent exposure was also found to be negligible. Bioavailability in exposure routes helps making adjustments to the risk prediction by avoiding the chance of overestimating or underestimating the hazard due to solvent exposure. Also, considering the bioavailability during risk assessment through different modes of exposure will help the risk evaluator to make appropriate decision in the abatement of hazard. Though both the deterministic as well as probabilistic methods were found to be equally good in determining the sensitive population and the critical exposure pathway, future studies should consider actual demographic data in the study area. Also, the studies can further be extended to toxicokinetic interaction modeling on risk estimation and uncertainty analysis. This study thus provides an insight to researchers of possible solvent contamination and the associated risk to human health.

**Authors' contributions** S. Mohan: Supervision, Writing - review & editing, Visualization. S. Sruthy: Methodology, Formal analysis, Data curation, Validation, Writing - original draft.

**Data Availability** All relevant data are included in the manuscript.

**Declaration**

**Conflict of Interest** The authors declare that no competing interests exist.

## References


Agrawal A, Kumari S, Sahu KK (2011) Studies on solvent extraction of iron (III ) as a step for conversion of a waste effluent to a value added product. J Environ Manage 92:3105–3111. https://doi.org/10.1016/j.jenvman.2011.07.026

Akdeniz N, Jacobson LD, Hetchler BP (2013) Health risk assessment of occupational exposure to hazardous volatile organic compounds in swine gestation, farrowing and nursery barns. Environ Sci Process Impacts 15:563–572. https://doi.org/10.1039/c2em30722g

Alidadi H, Sany SBT, Oftadeh BZG, Mohamad T, Shamszade H, Fakhari M (2019) Health risk assessments of arsenic and toxic heavy metal exposure in drinking water in northeast Iran. Environ Health Prev Med 24:1–17. https://doi.org/10.1186/s12199-019-0812-x

Bakhtavar E, Hosseini S, Hewage K, Sadiq R (2021) Air pollution risk assessment using a hybrid fuzzy intelligent probability-based approach: mine blasting dust impacts. Nat Resour Res 30:2607–2627. https://doi.org/10.1007/s11053-020-09810-4

Banton MI, Bus JS, Collins JJ, Delzell E, Gelbke HP, Kester JE, Moore MM, Waites R, Sarang SS (2019) Evaluation of potential health effects associated with occupational and environmental exposure to styrene–an update. J Toxicol Environ Heal - Part B Crit Rev doi. https://doi.org/10.1080/10937404.2019.1633718

Bearer C (1995) How are children different from adults? Environmental Health Perspectives. 103:7–12. https://doi.org/10.1289/ehp.95103s67

Blum KM, Andersson PL, Renman G, Ahrens L, Gros M, Wiberg K, Haglund P (2017) Non-target screening and prioritization of potentially persistent, bioaccumulating and toxic domestic wastewater contaminants and their removal in on-site and large-scale sewage treatment plants. Sci Total Environ 575:265–275. https://doi.org/10.1016/j.scitotenv.2016.09.135

Bramante CT, Spiller P, Landa M (2020) Fish consumption during pregnancy: An opportunity, not a risk. HHS Public Access 172:801–802. https://doi.org/10.1001/jamapediatrics.2018.1619

Bruce ED, Abusalih AA, McDonald TJ, Autenrieth RL (2007) Comparing deterministic and probabilistic risk assessments for sites contaminated by polycyclic aromatic hydrocarbons (PAHs). J Environ Sci Heal - Part A Toxic/Hazardous Subst. Environ Eng 42:697–706. https://doi.org/10.1080/10934520701304328

Caetano T, Branco V, Cavaco A, Carvalho C (2019) Risk assessment of methylmercury in pregnant women and newborns in the island of Madeira (Portugal) using exposure biomarkers and food-frequency questionnaires. J Toxicol Environ Heal - Part A Curr Issues 82:833–844. https://doi.org/10.1080/15287394.2019.1658859

Carder M, Seed MJ, Money A, Agius RM, Van Tongeren M (2019) Occupational and work-related respiratory disease attributed to cleaning products. Occup Environ Med 76:530–536. https://doi.org/10.1136/oemed-2018-105646

Chance GW, Harmsen E (1998) Children are different: environmental contaminants and children's health. Can J Public Health. 89 Suppl 1:S9-S15. http://www.ncbi.nlm.nih.gov/pubmed/9654786

Changing Markets Foundation (2018) Hyderabad's pharmaceutical pollution crisis: Heavy metal and solvent contamination at factories in a major Indian drug manufacturing hub. http://www.changingmarkets.org/(Accessed on 20 June 2021)

Clemens RT (1996) Hard Decisions: An Introduction to Decision Analysis. Duxbury Press, Pacific Grove, CA, pp 410–426

Collier AC (2007) Pharmaceutical contaminants in potable water: Potential concerns for pregnant women and children. Ecohealth 4:164–171. https://doi.org/10.1007/s10393-007-0105-5

Ershow AG, Brown LM, Cantor KP (1991) Intake of tapwater and total water by pregnant and lactating women. Am J Public Health 81:328–334. https://doi.org/10.2105/AJPH.81.3.328

Fallahzadeh RA, Miri M, Taghavi M, Gholizadeh A, Anbarani R, Hosseini-Bandegharaei A, Ferrante M, Oliveri Conti G (2018) Spatial variation and probabilistic risk assessment of exposure to fluoride in drinking water. Food Chem Toxicol 113:314–321. https://doi.org/10.1016/j.fct.2018.02.001

Fan C, Wang GS, Chen YC, Ko CH (2009) Risk assessment of exposure to volatile organic compounds in groundwater in Taiwan. Sci Total Environ 407:2165–2174. https://doi.org/10.1016/j.scitotenv.2008.12.015

Felter SP, Daston GP, Euling SY, Piersma AH, Tassinari MS (2015) Assessment of health risks resulting from early-life exposures: Are current chemical toxicity testing protocols and risk assessment methods adequate? Crit Rev Toxicol doi. https://doi.org/10.3109/10408444.2014.993919

Gago-Ferrero P, Gros M, Ahrens L, Wiberg K (2017) Impact of on-site, small and large scale wastewater treatment facilities on levels and fate of pharmaceuticals, personal care products, artificial sweeteners, pesticides, and perfluoroalkyl substances in recipient waters. Sci Total Environ 601–602:1289–1297. https://doi.org/10.1016/j.scitotenv.2017.05.258

García V, Pongrácz E, Phillips PS, Keiski RL (2013) From waste treatment to resource efficiency in the chemical industry: recovery of organic solvents from waters containing electrolytes by pervaporation. J Clean Prod 39:146–153. https://doi.org/10.1016/j.jclepro.2012.08.020

Ghosh SP, Raj D, Maiti SK (2020) Risks assessment of heavy metal pollution in roadside soil and vegetation of national highway crossing through industrial area. Environ Process 7:1197–1220. https://doi.org/10.1007/s40710-020-00463-2

Girish CR, Murty VR (2015) Adsorption of phenol from aqueous solution using *Lantana camara*, forest waste: packed bed studies and prediction of breakthrough curves. Environ Process 2:773–796. https://doi.org/10.1007/s40710-015-0117-z

Guerra F, Trevizam AR, Muraoka T, Marcante NC, Canniatti-Brazaca SG (2012) Heavy metals in vegetables and potential risk for human health. Sci Agric 69:54–60. https://doi.org/10.1590/S0103-90162012000100008

Guissouma W, Hakami O, Al-rajab AJ, Tarhouni J (2017) Risk assessment of fluoride exposure in drinking water of Tunisia. Chemosphere 177:102–108. https://doi.org/10.1016/j.chemosphere.2017.03.011

Guleria A, Chakma S (2021) Probabilistic human health risk assessment of groundwater contamination due to metal leaching: A case study of Indian dumping sites. Hum Ecol Risk Assess. 27:101–133. https://doi.org/10.1080/10807039.2019.1695193

Guo G, Zhang D, Wang Y (2019) Probabilistic human health risk assessment of heavy metal intake via vegetable consumption around Pb/Zn smelters in Southwest China. Int. J. Environ. Res. Public Health 16:3267. https://doi.org/10.3390/ijerph16183267

Guyton KZ, Hogan KA, Scott CS, Cooper GS, Bale AS, Kopylev L, Barone S, Makris SL, Glenn B, Subramaniam RP, Gwinn MR, Dzubow RC, Chiu WA (2014) Human health effects of tetrachloroethylene: Key findings and scientific issues. Environ Health Perspect 122(4):325–334. https://doi.org/10.1289/ehp.1307359

Howard PH, Muir DCG (2013) Identifying new persistent and bioaccumulative organics among chemicals in commerce: Byproducts, impurities, and transformation products. Environ Sci Technol 47:5259–5266. https://doi.org/10.1021/es4004075

Hu G, Bakhtavar E, Hewage K, Mohseni M, Sadiq R (2019) Heavy metals risk assessment in drinking water: An integrated probabilistic- fuzzy approach. J Environ Manage 250:109514. https://doi.org/10.1016/j.jenvman.2019.109514

IARC (2021) International Agency for Research on Cancer, Agency of World Health Organization. https://www.iarc.who.int/. (Accessed on 25 June 2021)

IPCS (2010) International Programme on Chemical Safety, WHO human health risk assessment toolkit: chemical hazards. https://apps.who.int/iris/handle/10665/44113 (Accessed on 25 June 2021)

IRIS (2019) Integrated Risk Information System. US Environmental Proctection Agency, Washington, DC. https://www.epa.gov/iris/. (Accessed on 25 June 2021)

Jimenez-Oyola S, Escobar Segovia K, García-Martínez MJ, Ortega M, Bolonio D, García-Garizabal I, Salgado B (2021) Human health risk assessment for exposure to potentially toxic elements in polluted rivers in the ecuadorian amazon. Water 13:613. https://doi.org/10.3390/w13050613

Jukic AM, Baird DD, Weinberg CR, McConnaughey DR, Wilcox AJ (2013) Length of human pregnancy and contributors to its natural variation. Hum Reprod 28:2848–2855. https://doi.org/10.1093/humrep/det297

Kanwar P (2018) Ecological risk in the anthropocene: an evaluation of theory, values, and social construct. Encyclopedia of the Anthropocene 4:367–372. https://doi.org/10.1016/B978-0-12-809665-9.10487-2

Karunathilake H, Bakhtavar E, Chhipi-Shrestha G, Mian H, Hewage K, Sadiq R (2020) Decision making for risk management: A multi-criteria perspective. Methods in Chemical Process Safety.:239–287. https://doi.org/10.1016/bs.mcps.2020.02.004

Kaur L, Rishi MS, Siddiqui AU (2020) Deterministic and probabilistic health risk assessment techniques to evaluate non-carcinogenic human health risk (NHHR) due to fluoride and nitrate in groundwater of Panipat, Haryana, India. Environ Pollut 259:113711. https://doi.org/10.1016/j.envpol.2019.113711

Kortei NK, Heymann ME, Essuman EK, Kpodo FM, Akonor PT, Lokpo SY, Boadi NO, Ayim-Akonor M, Tettey C (2020) Health risk assessment and levels of toxic metals in fishes (Oreochromis noliticus and Clarias anguillaris) from Ankobrah and Pra basins: Impact of illegal mining activities on food safety. Toxicol Reports 7:360–369. https://doi.org/10.1016/j.toxrep.2020.02.011

Kumar A, Chang B, Xagoraraki I (2010) Human health risk assessment of pharmaceuticals in water: Issues and challenges ahead. Int J Environ Res Public Health 7:3929–3953. https://doi.org/10.3390/ijerph7113929

Lando AM, Fein SB, Choinière CJ (2012) Awareness of methylmercury in fish and fish consumption among pregnant and postpartum women and women of childbearing age in the United States. Environ Res 116:85–92. https://doi.org/10.1016/j.envres.2012.04.002

Lee LJH, Chan CC, Chung CW, Yee-Chung WGS, Wang J (2002) Health risk assessment on residents exposed to chlorinated hydrocarbons contaminated in groundwater of a hazardous waste site. J Toxicol Environ Heal - Part A 65:219–235. https://doi.org/10.1080/15287390252800828

Liao VHC, Chou WC, Chio CP, Ju YR, Liao CM (2010) A probabilistic approach to quantitatively assess the inhalation risk for airborne endotoxin in cotton textile workers. J Hazard Mater 177:103–108. https://doi.org/10.1016/j.jhazmat.2009.11.151

Lundqvist A, Johansson I, Wennberg AL, Hultdin J, Högberg U, Hamberg K, Sandström H (2014) Reported dietary intake in early pregnant compared to non-pregnant women - A cross-sectional study. BMC Pregnancy Childbirth 14:373. https://doi.org/10.1186/s12884-014-0373-3

LuoY GW, Ngo HH, Nghiem LD, Hai FI, Zhang J, Liang S, Wang XC (2014) A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. Sci Total Environ 473–474:619–641. https://doi.org/10.1016/j.scitotenv.2013.12.065

Maxwell O, Olusegun OA, ESB J II, Mary AT, Emeka EO, Uchechukwu OA, Adeleye BN, Michael OM (2021) measurements of seasonal variations of radioactivity distributions in riverine soil sediment of Ado-Odo Ota. South-West Nigeria: Probabilistic approach using Monte Carlo 193:76–89. https://doi.org/10.1093/rpd/ncab027

Modla G, Lang P (2012) Removal and recovery of organic solvents from aqueous waste mixtures by extractive and pressure swing distillation. Ind Eng Chem Res 51:11473–11481. https://doi.org/10.1021/ie300331d

Narciso L, Catone T, Aquilina G, Attias L, De Angelis I, Iuliano MG, Tassinari R, Mantovani A, Maranghi F (2017) The juvenile toxicity study as a tool for a science-based risk assessment in the children population group. Reproductive Toxicology 72:136–141. https://doi.org/10.1016/j.reprotox.2017.06.188

Narsimha A, Sudarshan V (2017) Contamination of fluoride in groundwater and its effect on human health: a case study in hard rock aquifers of Siddipet, Telangana State, India. Appl Water Sci 7:2501–2512. https://doi.org/10.1007/s13201-016-0441-0

Ndikom CM, Fawole B, Ilesanmi RE (2014) Extra fluids for breastfeeding mothers for increasing milk production. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD008758.pub2

Noutsopoulos C, Charalambous V, Koumaki E (2020) evaluating the fate of emerging contaminants in wastewater treatment plants through plant-wide mathematical modelling. Environ Process 7:1065–1094. https://doi.org/10.1007/s40710-020-00459-y

Ofori SA, Cobbina SJ, Imoro AZ, Doke DA, Gaiser T (2021) Polycyclic aromatic hydrocarbon (pah) pollution and its associated human health risks in the Niger Delta Region of Nigeria: a systematic review. Environ Process 8:455–482. https://doi.org/10.1007/s40710-021-00507-1

Orosun MM (2021) Assessment of arsenic and its associated health risks due to mining activities in parts of North-central Nigeria: Probabilistic approach using Monte Carlo. J Hazard Mater 412:125262. https://doi.org/10.1016/j.jhazmat.2021.125262

Orosun MM, Adewuyi AD, Salawu NB, Isinkaye MO, Orosun OR, Oniku AS (2020) Monte Carlo approach to risks assessment of heavy metals at automobile spare part and recycling market in Ilorin, Nigeria. Sci Rep 10:22084. https://doi.org/10.1038/s41598-020-79141-0

Pirsaheb M, Hadei M, Sharafi K (2021) Human health risk assessment by Monte Carlo simulation method for heavy metals of commonly consumed cereals in Iran- Uncertainty and sensitivity analysis. J. Food Compos. Anal. 96:103697. https://doi.org/10.1016/j.jfca.2020.103697

Pitiriciu M, Tansel B (2021) Volatile organic contaminants (VOCs) emitted from sewer networks during wastewater collection and transport. J Environ Manage 285:112136. https://doi.org/10.1016/j.jenvman.2021.112136

RAIS (2019) The Risk Assessment Information System: Toxicity Values and Physical Parameters. https://rais.ornl.gov/cgi-bin/tools/TOX_search. (Accessed 25 June 2021)

Rajasekhar B, Nambi IM, Govindarajan SK (2018) Human health risk assessment of ground water contaminated with petroleum PAHs using Monte Carlo simulations: A case study of an Indian metropolitan city. J Environ Manage 205:183–191. https://doi.org/10.1016/j.jenvman.2017.09.078

Raju A, Singh A (2017) Assessment of groundwater quality and mapping human health risk in Central Ganga Alluvial Plain, Northern India. Environ. Process. 4:375–397. https://doi.org/10.1007/s40710-017-0232-0

Ramirez N, Marcé RM, Borrull F (2011) Determination of volatile organic compounds in industrial wastewater plant air emissions by multi-sorbent adsorption and thermal desorption-gas chromatography-mass spectrometry. Intern. J Environ Anal Chem 91:10–20. https://doi.org/10.1080/03067310903584073

Rees D, Soderlund N, Cronje R, Song E, Kielkowski D, Myers J (1993) Solvent exposure, alcohol consumption and liver injury in workers manufacturing paint. Scand J Work Environ Heal 19:236–244. https://doi.org/10.5271/sjweh.1478

Rishi MS, Kaur L, Sharma S (2020) Groundwater quality appraisal for non-carcinogenic human health risks and irrigation purposes in a part of Yamuna sub-basin. India. Hum. Ecol. Risk Assess. 26:2716–2736. https://doi.org/10.1080/10807039.2019.1682514

Rudel H, Körner W, Letzel T, Neumann M, Nödler K, Reemtsma T (2020) Persistent, mobile and toxic substances in the environment: a spotlight on current research and regulatory activities. Environ. Sci. Eur. 32:5. https://doi.org/10.1186/s12302-019-0286-x

Saleh HN, Panahande M, Yousefi M, Asghari FB, Oliveri Conti G, Talaee E, Mohammadi AA (2019) Carcinogenic and non-carcinogenic risk assessment of heavy metals in groundwater wells in Neyshabur Plain, Iran. Biol Trace Elem Res 190:251–261. https://doi.org/10.1007/s12011-018-1516-6

Santacruz A, Collado MC, García-Valdés L, Segura MT, Marítn-Lagos JA, Anjos T, Martí-Romero M, Lopez RM, Florido J, Campoy C, Sanz Y (2010) Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr. 104:83–92. https://doi.org/10.1017/S0007114510000176

Shi M, Zhang R, Wang Y, Zhang Y, Zhang Y, Zhang Y (2020) Health risk assessments of polycyclic aromatic hydrocarbons and chlorinated/brominated polycyclic aromatic hydrocarbons in urban air particles in a haze frequent area in China. Emerg Contam 6:172–178. https://doi.org/10.1016/j.emcon.2020.04.002

Shokoohi R, Khazaei M, Karami M, Seid-Mohammadi A, Khotanlou H, Berijani N, Torkshavand Z (2021) Deterministic and probabilistic human health risk assessment approach of exposure to heavy metals in drinking water sources: A case study of a semi-arid region in the west of Iran. J Environ Health Sci Engineer 19:1047–1055. https://doi.org/10.1007/s40201-021-00671-4/Published

Silver E, Kaslow J, Lee D, Lee S, Lynn M, Weis E, Ujihara A (2007) Fish consumption and advisory awareness among low-income women in California's Sacramento – San Joaquin Delta. Environmental Research 104:410–419. https://doi.org/10.1016/j.envres.2007.03.003

Singh G, Rishi MS, Herojeet R, Kaur L, Sharma K (2020) Evaluation of groundwater quality and human health risks from fluoride and nitrate in semi-arid region of northern India. Environ Geochem Health 42:1833–1862. https://doi.org/10.1007/s10653-019-00449-6

Sorengard M, Campos-Pereira H, Ullberg M, Lai FY, Golovko O, Ahrens L (2019) Mass loads, source apportionment, and risk estimation of organic micropollutants from hospital and municipal wastewater in recipient catchments. Chemosphere 234:931–941. https://doi.org/10.1016/j.chemosphere.2019.06.041

Sparkman OD, Penton ZE, Kitson FG (2011). Gas Chromatography and Mass Spectrometry (Second Edition) Academic Press. 15-83. ISBN 9780123736284. https://doi.org/10.1016/B978-0-12-373628-4.00002-2

Srinivasan R, Rajasekhar B, Nambi IM (2021) Deterministic and probabilistic health risk assessment for exposure to non-steroidal anti-inflammatory drugs in an Indian river. Environ Sci Pollut Res. 28:39826–39839. https://doi.org/10.1007/s11356-020-11897-4

Trommer H, Neubert RHH (2006) Overcoming the stratum corneum: The modulation of skin penetration. A review. 19:106–121. https://doi.org/10.1159/000091978

Ukai H, Takada S, Inui S, Imai Y, Kawai T, Shimbo SI, Ikeda M (1994) Occupational exposure to solvent mixtures: effects on health and metabolism. Occupational and Environmental Medicine. 51:523–529. https://doi.org/10.1136/oem.51.8.523

US EPA (1989) Risk Assessment Guidance for Superfund. Volume I (Part A). Human Health Evaluation Manual. EPA/540/1-89/002Washington, D.C. Office of Emergency and Remedial Response US Environmental Protection Agency.

US EPA (2000) Guidance for assessing chemical contaminant data for use in fish advisories. Volume II. Risk assessment and fish consumption limits. 3rd ed. EPA 823-B-00-008

US EPA (2001) Risk Assessment Guidance for Superfund: Volume III (Part A). Process for Conducting Probabilistic Risk Assessment. Office of Emergency and Remedial Response. US Environmental Protection Agency, Washington, DC, EPA 540-R-02-002 OSWER 9285.7-45 PB2002 963302

US EPA (2003) Method 5030C (SW-846): Purge-and-Trap for Aqueous Samples. Revision 3. United States Environmental Protection Agency, Washington, DC

US EPA (2004) Risk Assessment: Guidance for Superfund Volume I. Human Heatlh Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment) Final Office of Superfund Remediation and Technology Innovation US Environmental Protection Agency Washington, DC, EPA/540/R/99/005 OSWER 9285.7-02EP PB99-963312 July 2004

US EPA (2005) Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. Risk Assessment Forum US Environmental Protection Agency, Washington, DC, EPA/630/P-03/003F

US EPA (2011) Exposure Factors Handbook 2011 Edition (Final Report). U.S. Environmental Protection Agency, Washington DC, EPA/600/R-09/052F, 2011

Vandenplas O, D'Alpaos V, Evrard G, Jamart J, Thimpont J, Huaux F, Renauld JC (2013) Asthma related to cleaning agents: A clinical insight. *BMJ Open* 3:e003568. https://doi.org/10.1136/bmjopen-2013-003568

Wang CC, Niu ZG, Zhang Y (2013a) Health risk assessment of inhalation exposure of irrigation workers and the public to trihalomethanes from reclaimed water in landscape irrigation in Tianjin, North China. J Hazard Mater 262:179–188. https://doi.org/10.1016/j.jhazmat.2013.08.044

Wang CC, Niu ZG, ZhangY (2013b) Health risk assessment of inhalation exposure of irrigation workers and the public to trihalomethanes from reclaimed water in landscape irrigation in Tianjin, North China. J Hazard Mater 262:179–188. https://doi.org/10.1016/j.jhazmat.2013.08

WHO (2017) Guidelines for Drinking-water Quality. Volume IV. ISBN: 978-92-4-154995-0 https://www.who.int/publications/i/item/9789241549950 (Accessed on 10 June 2021)

Wolterink GA, Piersma A, Van Engelen J (2002) Risk assessment of chemicals: What about children?, RIVM report 613340005. https://www.rivm.nl/bibliotheek/rapporten/613340005.pdf (Accessed on 12 July 2021)

Wong MH, Armour MA, Naidu R, Man M (2012) Persistent toxic substances: Sources, fates and effects. Rev Environ Health 27:207–213. https://doi.org/10.1515/reveh-2012-0040

Wu B, Zhang Y, Zhang XX, Cheng SP (2011) Health risk assessment of polycyclic aromatic hydrocarbons in the source water and drinking water of China: Quantitative analysis based on published monitoring data. Sci Total Environ 410–411:112–118. https://doi.org/10.1016/j.scitotenv.2011.09.046

Yang C, Xiao Z, Ho S, Wu T, Tsai S (2007) Association between trihalomethane concentrations in drinking water and adverse pregnancy outcome in Taiwan. Environ Res 104(3):390–395. https://doi.org/10.1016/j.envres.2007.01.006

Zhang L, Huang D, Yang J, Wei X, Qin J, Ou S, Zhang Z, Zou Y (2017) Probabilistic risk assessment of Chinese residents' exposure to fluoride in improved drinking water in endemic fluorosis areas. Environ. Pollut. 222:118–125. https://doi.org/10.1016/j.envpol.2016.12.074

Zhang Y, Xu B, Guo Z, Han J, Li H, Jin L, Chen F, Xiong Y (2019) Human health risk assessment of groundwater arsenic contamination in Jinghui irrigation district, China. J Environ Manag 237:163–169. https://doi.org/10.1016/j.jenvman.2019.02.067

Zhou Y, Zhu X, Qin Y, Li Y, Zhang M, Liu W, Huang H, Xu Y (2019) Association between total water intake and dietary intake of pregnant and breastfeeding women in China: A cross-sectional survey. BMC Pregnancy Childbirth 19:1–10. https://doi.org/10.1186/s12884-019-2301-z