



Uncertainties in age- and gender-based health risk assessment for recreational bathing: Arsenic in Del Azul stream, Argentina

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ABSTRACT

The aim of this study was to assess the risk associated with recreational bathing at Del Azul stream, Argentina, a water course naturally containing Arsenic. It represents a case study on the carcinogenic risk for bathers and on how the risk varies among age groups and genders, analyzing the uncertainties of the model input variables and the risk quantification technique. The risk was probabilistically estimated with the 2D Monte Carlo method considering four age groups (5, 10, 15, and 20 years old) and separate exposure routes: accidental water intake, skin contact, and the two combined. Although in all the studied groups the risk levels were within safety limits, differences in risk values were observed among age groups and genders. Accidental water intake during bathing was the most risky exposure route. The risk decreased with age and it was higher in males than in females, with larger differences between the two older age groups. This could be attributed to the difference in the accidental water intake rate associated with the daily duration of the bathing event, which varied according to age and gender.

ARTICLE HISTORY

Received 3 June 2015
Revised manuscript
accepted 9 October 2015

KEYWORDS

Arsenic water pollution; bathing activities; cancer risk; uncertainty; age and gender variability

Introduction

Health Risk Assessment (HRA) constitutes a management tool that is becoming increasingly important in pollution analysis. Among the most frequent HRA uses are the estimation of health risk under different scenarios of exposure to toxic substances in order to determine health effects and to aid in the setting of legal threshold limits (Falk-Filipsson *et al.* 2007).

Uncertainty and variability are inherent in HRA (Bogen 1990; Finkel 1990; Carrington and Bolger 1998; Cullen and Frey 1999). Studies on uncertainty and variability are often found in the HRA literature whether considering input variables or scenarios of exposure (*e.g.*, Carrington and Bolger 1998; Hertwich *et al.* 1999; Binkowitz and Wartenberg 2001; Glorennec 2006; Benekos *et al.* 2007; Filipsson *et al.* 2011), models architecture (*e.g.*, Slob 1994; Hertwich *et al.* 2000; Moschandreas and Karuchit 2002; Falk-Filipsson *et al.* 2007; Ascow II *et al.* 2008), and

physiological or toxicological aspects (e.g., Calabrese 1985; Hattis *et al.* 1987; Calabrese and Baldwin 1995; Dourson *et al.* 1996; Renwick and Lazarus 1998; Dourson *et al.* 2002; Lipscomb *et al.* 2004). Uncertainty and variability are different concepts. Uncertainty refers to the lack of knowledge about something due to incomplete data, errors and biases, randomness, and so on, also called “epistemic uncertainty.” Variability, in contrast, is a type of uncertainty caused by natural heterogeneity and could be called “stochastic variability.” Because frequently the environmental data is qualitative, vague, or imprecise (Darbra *et al.* 2008), the identification and quantification of the uncertainty should always be considered in this type of analysis. For this reason “proper evaluation of uncertainties has become a major concern in environmental and health risk assessment studies” (Kentel and Aral 2007, p 405). Among the techniques used to quantify uncertainty, two of the most frequently used are the probabilistic and the fuzzy-set (Kentel and Aral 2007; Darbra *et al.* 2008), with the former being more frequently used than the latter (Darbra *et al.* 2008).

Among research works on HRA in which the uncertainty is considered, some are related to pollutant exposure through water intake either during residential (e.g., Phang *et al.* 2010; Wang *et al.* 2011) or recreational bathing scenarios (e.g., Filipsson *et al.* 2009; Schets *et al.* 2011). Similarly, there are studies on airborne pollutants that consider the effect of the breathing rate (e.g., Guo *et al.* 2004; Shi *et al.* 2009) or on pollutants in the food that consider the effect of the ingestion rate (e.g., Obiri *et al.* 2006; Liu *et al.* 2011a), or studies which consider several simultaneous routes of exposure (e.g., Zheng *et al.* 2010; Liu *et al.* 2011b). However, the primary focus of those mentioned studies was to find differences in exposure between children and adults or, much less frequently, among other age groups and genders. Indeed, only few studies considered the variation in the exposure patterns due to age (e.g., Zhao and Kaluarachchi 2002; Liao and Chiang 2006; Benekos *et al.* 2007). Nevertheless, no HRA studies were found in which age and gender were simultaneously considered and in which the impact on the uncertainty was measured.

The purpose of this study was to contribute to the progress on the HRA methodology development associated with recreational bathing in natural waters by estimating the carcinogenic probabilistic health risk due to Arsenic (As) exposure. The main objective was to quantify the As cancer health risk differentiating among age groups and between genders analyzing (1) the effect of the probabilistic method applied on the risk results and (2) the effect of considering the epistemic and stochastic uncertainty due to age and gender on the risk results. In addition, a comparative analysis considering the results of a previous study (Peluso *et al.* 2012) was carried out.

Methodology

Study background

Peluso *et al.* (2012) estimated the cumulative cancer and non-cancer health risk in bathers exposed to several toxic substances in natural waters used for recreational bathing. Those substances were mainly heavy metals (As, Cu, Cr, Hg, Zn) and pesticides (α -, β -, γ -, and δ -HCH, Aldrin, γ -Chlordane, Chlorpyrifos, Cypermethrin, Endosulfan, Endosulfan Sulphate, Glyphosate, and Heptachlor). That study considered an aggregated exposure route through accidental water intake and dermal contact and, calculated the risk for each of four age groups (*i.e.*, 5, 10, 15, and 20 years old) using the USEPA model (1989, 1992a, 1992b,

2004). Those results showed that the cancer and non-cancer risk values were uncritical in all age groups. As was the most risky non-pesticide toxic chemical by cancer and non-cancer effects. That study revealed that there were significant differences among age groups and that the exposure input variables related to the bathing behavior had the greatest influence on the risk outcome. Although that study addressed the risk uncertainty applying the probabilistic method, two aspects related to uncertainty quantification were not considered in it. First, it did not differentiate between epistemic uncertainty and stochastic variability in input variables. Second, that study did not address the effect of gender within each age group. In this study we are attempting to identify the most vulnerable subpopulation considering age groups and genders, taking into account the impact of the uncertainty on the risk results during recreational bathing at Del Azul stream.

HRA methodology

The exposure through accidental water intake and dermal contact during recreational bathing was quantified based on the USEPA model applying Eqs. (1) and (2), respectively (USEPA 1992a, 1992b, 2004).

$$ADDI = [Conc * Ir * EF * ED] / [Bw * AT] \quad (1)$$

$$ADDS = [DAevent * ESA * EF * ED * FC] / [Bw * AT] \quad (2)$$

where ADDI = Average daily dose by accidental intake ($\text{mg kg}^{-1} \text{ day}^{-1}$); ADDS = Average daily dose by skin contact ($\text{mg kg}^{-1} \text{ day}^{-1}$); *Conc* = Concentration of As in water (mg L^{-1}); *Ir* = Daily rate of water accidental intake (L day^{-1}); *EF* = Annual exposure frequency of bathing activities (days year^{-1}); *ED* = Exposure duration (year); *BW* = Body Weight of the exposed human (kg); *AT* = Correction factor for chronic exposure during lifetime ($70 * 365$ days for cancer risk estimation); *DAevent* = Skin absorbed dose per event ($\text{mg cm}^{-2} \text{ event}^{-1}$), based on USEPA (2007); *ESA* = Exposed skin area (cm^2); *FC* = Correction factor for surface and volume units ($10,000 \text{ cm}^2 \text{ m}^{-2} * 0.001 \text{ L cm}^{-3}$). These variables are described in the following paragraphs.

Cancer risk (CR) was obtained by multiplying the average daily dose (ADD) by a toxicological reference value, the Slope Factor (SF) (USEPA 1989). The SF for As is $1.5 (\text{mg / kg day})^{-1}$ according to the USEPA (2014). A maximum value of 10E^{-05} was assumed as the CR safety limit (Peluso *et al.* 2012).

All the exposure input variables were given a probabilistic treatment by (1) using the probability density function (PDF) that best fit our data applying Crystal Ball 7.1 software (Decisioneering 2007), (2) using PDFs based on literature, or (3) generating PDFs suitable for the selected scenarios. The approach used in any case is further explained in the following sections for each input variable. The risk was initially estimated by applying the Monte Carlo (MC) simulation method for simple random sampling (one-dimensional MC procedure or 1D MC) set at 5000 iterations, using Crystal Ball 7.1 software (Decisioneering 2007). This model generates simultaneous random iterations for each ADD input variable and calculates the risks based on Eqs. (1) and (2). The results are new CR PDFs containing the uncertainty of the input variables.

In addition, another type of the MC method that allows distinguishing between input variables with epistemic and stochastic uncertainty was applied, using the two-dimensional MC simulation procedure (2D MC). It consists in iterative runs of the whole model (*i.e.*, inner loops) to simulate the variability while keeping constant the epistemic uncertainty values (*i.e.*, outer loops). This process, repeated a certain number of times (5000) for some number of outer simulations (500), portrays how the forecast distribution varies according to uncertainty (Decisioneering 2007). Before applying this method, we had to choose the outer variables of the model, as explained further below. The 2D CR result is the arithmetic mean of the statistical descriptors (the 95th percentile, in this case) from the group of 500 CR PDFs. The main results of the whole study were obtained with the 2D MC approach whereas the 1D MC was used to estimate threshold values for comparative purposes and to estimate the uncertainty by comparing the 1D versus 2D MC results.

The exposed individuals were grouped into four age categories (5, 10, 15, and 20 years old) and further sub grouped by gender: males (M) and females (F). The 20-year-old age group also includes data of older individuals due to morphometric differences in adults of different ages are less conspicuous than in children. Each target group 2D CR was individually calculated for each exposure route (oral and dermal) and for both routes combined (aggregated exposure). In the latter case, an additive risk index was utilized during the MC iterations thus resulting in a new CR PDF.

Arsenic concentration

The concentration PDF used for exposure calculation was obtained from 96 samples bimonthly collected between December 2005 and December 2007 at Del Azul stream. Peluso *et al.* (2012) provided a detailed description of the study area. Sampling was performed during dry periods (lack of rain at least within five days before sampling). Water samples were taken at the subsurface level (approximately 30 cm below water level) in the middle of the watercourse and collected in high-density polyethylene bottles with internal Teflon tops. The water samples were kept at 4°C until analyzed.

The concentration of As was measured using a VARIAN SPECTRAA55 absorption atomic spectrophotometer, and a VGA-77 Cold Vapor Generator, according to USEPA's SW 846 and M 7061A methods, respectively.

The best fit As PDF (*Conc* in Eq. [1]) was obtained using Crystal Ball 7.1 (Decisioneering 2007) by applying the Anderson Darling goodness-of-fit test. The software matches the concentration data against several theoretical continuous probability distributions and finds the one that best fits our observational data distribution. In all the water samples, there were non-detect concentrations. These were replaced by the 95% Upper Confidence Limit (UCL) of the arithmetic mean of the detected concentrations. The 95% UCL of a mean is a value that, when calculated for a random data set, equals or exceeds the true mean 95% of the times (USEPA 1992b). The UCL estimation was performed using ProUCL 4.1 software (USEPA 2010), which carries out a number of UCL parametric and distribution-free non-parametric methods, and recommends the one most appropriate to use based on the distribution of the data.

The best fit As PDF was the Beta ($\alpha = 1.29$ and $\beta = 3.07$) with the following descriptive statistical parameter values: minimum: 10.0; maximum: 60.0; arithmetic mean: 28.4; median: 26.5; standard deviation: 12.3; 95th percentile: 51.7, all measured in $\mu\text{g L}^{-1}$.

Other input variables of the exposure model

The accidental water intake rate [Ir from Eq. (1)] for all age groups and genders was based on Dufour *et al.* (2006). However, we assigned the Normal distribution as the PDF for Ir in all age groups and genders. For boys (5, 10, and 15 years old) that distribution had a mean of 60 mL h^{-1} with a standard deviation equal to 1, and it was truncated at 210 mL h^{-1} . For girls, the mean was 40 mL h^{-1} , with the same standard deviation and point of truncation values as for boys. For men, the mean and the standard deviation were the same as for boys, but the curve was truncated at 70 mL h^{-1} . For women, the mean was 30 mL h^{-1} , with the standard deviation and curve truncation point being the same as for men.

The absorbed dermal dose per event [DA_{event} from Eq. (2)] was calculated based on a USEPA model (USEPA 2007) as the product of the As concentration, the bathing event duration (T_{event} , in min d^{-1}), and the dermal permeability coefficient ($1.00\text{E}^{-03} \text{ cm h}^{-1}$) according to USEPA (2004). T_{event} and the bath frequency during the year [EF from Eqs. (1) and (2)] were estimated based on a questionnaire administered to about 2000 randomly selected visitors at the Del Azul bath resort (artificial beach for public use) during the 2010–2011 (Peluso *et al.* 2012) and 2011–2012 summers (unpublished). Adults answered on behalf of the children and teenagers that were with them. The survey was conducted until 250 responses were reached for each age and gender group. It considered personal information such as gender, age, and family composition. Some of the questions were about the number of visits to the resort during the surveyed summers; if the visitors were bathers or not; and how long bathers stayed in the water, among others. As implied above, the answers were grouped by gender into the four age groups.

T_{event} and EF for each age and gender group were probabilistically established based on the survey responses using the best-fit method with the aid of Crystal Ball 7.1 software (Decisioneering 2007). The maximum number of bath days (*i.e.*, days suitable for bathing) was not established by looking at the survey responses but rather by calculating the number of days with temperatures higher than 27°C and without rain episodes during the whole day, according to a local weather database (BDH 2012).

The duration of exposure [ED from Eqs. (1) and (2)] was probabilistically treated, assuming a triangular PDF with the lower and upper limits of 1 and 30 years, respectively, and 15 years as the mode, which was common to the four age groups and genders (Peluso *et al.* 2012). In the absence of a local study on this input variable, the maximum value of the assumed ED PDF was the default value taken from USEPA (2008).

The bathers' body weight and height [BW and H from Eqs. (1) and (2)] PDF models estimated were based on Lejarraga and Orfila's (1987) anthropometric data for Argentina's population.

The exposed body surface area was estimated by applying the DuBois and DuBois (1916) model, which is given in Eq. (3).

$$BSA = H^{0.725} \times BW^{0.425} \times 0.007184 \quad (3)$$

where BSA : Body Surface Area (cm^2), H : height (cm), BW : Body weight (kg).

However, to estimate the body surface area actually exposed for use in ADDS estimation, a correction factor called Bath Pattern (BP) was applied (Peluso *et al.* 2012). BP was

estimated as the percentage of the skin surface in contact with the water during the bathing event. The adjusted exposed surface area value [ESA from Eq. (2)] was calculated as shown in Eq. (4).

$$ESA = BSA \times BP \quad (4)$$

where ESA : Exposed Surface Area (cm^2), BP : Bath Pattern (dimensionless).

BP was calculated as the percentage of the body remaining underwater during the bathing event based on USEPA's (2004) recommended values for surface area of body parts. The direct observation of bathers revealed that only during a brief interval the entire body is completely submerged (Peluso *et al.* 2012). Rather, during more than half of the time of the bathing event water is up to the waistline. For this reason, a triangular PDF was assumed in which the minimum value represents the percentage of the entire body surface attributed to the feet, the mode to that attributed to the feet + legs + hands, and the maximum to the entire body (100% by definition). BP was calculated considering age but not gender. Table 1 presents the parameters and values used for ESA , BSA , and BP estimations.

Statistical analysis

Comparison among CR PDFs estimated by 1D and 2D MC and comparison among the estimated uncertainty levels

This analysis was conducted on 5-year-old M and F since that age group had the greatest CR according to the previous study (Peluso *et al.* 2012). The comparison of CRs was done by analyzing the ratio between the 95th percentiles of the CR PDFs obtained by 1D and by 2D MC simulations for accidental water intake exposure. The difference in CRs between M and F was estimated as the percent change in the 95th percentile value between the 1D and the 2D MC CRs, one variable at a time, considering each input variable as an outer 2D variable (epistemic uncertainty variable). Then, the 2D CR was calculated simultaneously considering several input variables as outer 2D variables. The results of this comparison were used as indicators of the comparative uncertainty levels between MC methods, and they were the basis for choosing the set of outer variables for the subsequent 2D CR calculations. The use of the 95th percentile as the main descriptor of the CR PDF was based on the reason that it represents a *high-end* estimate of the risk "above the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest exposure" (NRC 1994, p 369). As it was indicated above, the 95th percentile of the 2D CR PDF (2D 95th percentile) is the mean of 500 95th percentile values obtained with the 2D MC procedure whereas the 95th percentile CR obtained with the 1D MC method is represented by the single value of the 95th percentile of the CR PDF.

CR comparison among age groups and genders

Although several statistical parameters were elucidated from the CR PDF obtained by 2D MC for each age and gender group due to accidental water intake, dermal contact and the aggregated (combined) exposure routes (*i.e.*, mean, standard deviation, 95th percentiles, and maximum values), the main descriptor considered was the 2D 95th percentile.

The comparisons were done by analyzing the ratio between the 2D 95th percentiles of each CR PDF. Mann-Whitney and Kruskal-Wallis tests were applied to detect statistically

Table 1. Best fitting probability distributions for each of the exposure input variables and values for their descriptive statistics according to age and gender.

Age	Gender	Param.	Fitted dist.	Min. ^a	Max. ^b	AM ^c	SD ^d	95 th p ^e	Others
5	M	Tevent ^f	Weibull	1.00E+00	3.00E+02	1.43E+02	7.67E+01	2.72E+02	Sc ^h 2.99E+02
		EF	Mx.Extr ^k	1.00E+00	5.40E+01	2.54E+01	1.42E+01	4.97E+01	Sc ^h 2.17E+01
		BW ^m	Normal	1.35E+01	2.55E+01	1.95E+01	2.50E+00	1.95E+01	
		H ⁿ	Normal	1.00E+02	1.18E+02	1.09E+02	4.12E+00	1.16E+02	
		BSA ^o	Beta	6.52E+03	8.71E+03	7.61E+03	3.99E+02	8.27E+03	α 4.82E+00
		BP ^p	Triangular	7.75E-02	9.96E-01	4.92E-01	1.91E-01	8.31E-01	Mo ^q 4.10E-01 Idem for females
		ESA ^r	Beta	5.90E+02	8.17E+03	3.74E+03	1.46E+03	6.33E+03	β 4.79E+00
		Tevent	Weibull	1.00E+00	3.00E+02	1.39E+02	7.60E+01	2.67E+02	β 4.18E+00
		EF	Mx.Extr	1.00E+00	5.40E+01	2.41E+01	1.37E+01	4.85E+01	Sc 2.91E+02
		BW	Normal	1.50E+01	2.40E+01	1.95E+01	2.08E+00	2.30E+01	Sc 1.97E+01
		H	Normal	9.80E+01	1.16E+02	1.07E+02	4.09E+02	1.14E+02	Sc 1.41E+03
		BSA	Weibull	6.38E+03	8.61E+03	7.50E+03	3.86E+02	8.14E+03	Sh 3.67E+00
10	M	ESA	Beta	5.66E+02	8.02E+03	3.67E+03	1.46E+03	6.24E+03	α 2.32E+00
		Tevent	Min.Extr ^s	1.00E+00	3.00E+02	1.87E+02	6.78E+01	2.83E+02	Like 2.22E+02
		EF	Gamma	1.00E+00	5.40E+01	2.25E+01	1.45E+01	4.92E+01	Sc 3.60E+01
		BW	Normal	2.35E+01	4.45E+01	3.36E+01	5.00E+00	4.12E+01	Sc 3.60E+01
		H	Normal	1.24E+02	1.48E+02	1.36E+02	5.38E+00	1.45E+02	Sc 1.41E+03
		BSA	Weibull	9.28E+03	1.33E+04	1.13E+04	7.22E+02	1.25E+04	β 2.53E+00
		BP	Triangular	7.67E-02	9.99E-01	4.87E-01	1.92E-01	8.36E-01	Sc 6.83E+01
		ESA	Beta	7.92E+02	1.24E+04	5.51E+03	2.17E+03	9.42E+03	Sc 6.83E+01
		Tevent	Beta	1.00E+00	3.00E+02	1.94E+02	5.52E+01	2.74E+02	Sc 3.60E+01
		EF	Weibull	1.00E+00	5.40E+01	2.39E+01	1.44E+01	4.92E+01	Sc 3.80E+01
		BW	Normal	2.30E+01	4.60E+01	3.46E+01	5.20E+00	4.31E+01	Sc 3.80E+01
		H	Normal	1.22E+02	1.48E+02	1.35E+02	5.89E+00	1.45E+02	Sc 3.80E+01
15	M	BSA	Beta	8.99E+03	1.36E+04	1.13E+04	8.08E+02	1.26E+04	α 4.86E+00
		ESA	Beta	8.83E+02	1.21E+04	5.51E+03	2.18E+03	9.44E+03	β 4.19E+00
		Tevent	Min.Extr	1.00E+00	3.00E+02	1.78E+02	7.22E+01	2.83E+02	β 4.82E+00
		EF	Mx.Extr	1.00E+00	5.40E+01	2.76E+01	1.41E+01	5.08E+01	Sc 8.31E+01
		BW	Normal	3.40E+01	7.40E+01	5.03E+01	7.83E+00	6.19E+01	Sc 2.37E+01
		H	Normal	1.50E+02	1.80E+02	1.65E+02	6.84E+00	1.77E+02	β 4.34E+00
		BSA	Beta	1.30E+04	1.96E+04	1.63E+04	1.21E+03	1.83E+04	Idem for females
		BP	Triangular	6.55E-02	9.89E-01	5.03E-01	1.91E-01	8.35E-01	β 4.59E+00
		ESA	Beta	1.00E+03	1.78E+04	8.20E+03	3.19E+03	1.39E+04	β 4.59E+00
		Tevent	Mx.Extr	1.00E+00	3.00E+02	1.02E+02	6.76E+01	2.36E+02	Sc 7.26E+01
		EF	Mx.Extr	1.00E+00	5.40E+01	2.47E+01	1.41E+01	4.92E+01	Sc 2.17E+01
		BW	Normal	4.11E+01	6.90E+01	5.50E+01	6.36E+00	6.58E+01	Sc 2.17E+01

(Continued)



Table 1. (Continued)

Age	Gender	Param.	Fitted dist.	Min. ^a	Max. ^b	AM ^c	SD ^d	95 th pe	Others
20	M	H	Normal	1.48E+02	1.72E+02	1.60E+02	5.40E+00	1.69E+02	
		BSA	Beta	1.32E+04	1.80E+04	1.56E+04	8.66E+02	1.70E+04	β 4.74E+00
		ESA	Beta	9.90E+02	1.75E+04	7.85E+03	3.01E+03	1.31E+04	α 3.18E+00 β 4.30E+00
		Tevent	Mx.Extr	1.00E+00	3.00E+02	6.24E+01	4.56E+01	1.51E+02	Like 3.31E+01 Sc 3.91E+01
		EF	Mx.Extr	1.00E+00	5.40E+01	2.36E+01	1.38E+01	4.84E+01	Like 1.50E+01 Sc 1.84E+01
		BW	Normal	5.00E+01	8.50E+01	6.55E+01	7.60E+00	7.85E+01	
		H	Normal	1.60E+02	1.86E+02	1.74E+02	5.51E+00	1.83E+02	
		BSA	Weibull	1.53E+04	2.06E+04	1.78E+04	9.30E+02	1.93E+04	Loc 1.46E+04 Sc 3.46E+03
		BP	Triangular	7.40E-02	9.89E-01	4.99E-01	1.89E-01	8.33E-01	Idem for females Sh 3.85E+00
		ESA	Beta	1.28E+03	1.87E+04	8.89E+03	3.40E+03	1.48E+04	α 2.90E+00 β 4.22E+00
F	F	Tevent	Mx.Extr	1.00E+00	3.00E+02	4.15E+01	3.32E+01	1.07E+02	Like 1.55E+01 Sc 2.83E+01
		EF	Log	1.00E+00	5.40E+01	2.46E+01	1.42E+01	4.94E+01	Sc 1.76E+01
		BW	Normal	4.30E+01	7.20E+01	5.57E+01	7.02E+00	6.82E+01	
		H	Normal	1.50E+02	1.73E+02	1.61E+02	5.44E+00	1.70E+02	
		BSA	Beta	1.32E+04	1.81E+04	1.57E+04	8.69E+02	1.71E+04	α 5.06E+00 β 4.69E+00
		ESA	Beta	1.06E+03	1.62E+04	7.82E+03	2.99E+03	1.30E+04	α 2.83E+00 β 4.08E+00

^aMinimum; ^bMaximum; ^cArithmetic mean; ^dStandard deviation; ^e95th percentile; ^fEvent duration (min); ^gLocation; ^hScale; ⁱShape; ^jExposure frequency (days); ^kMaximum extreme; ^lLikeliest; ^mBody weight (kg); ⁿBody height (cm); ^oBody surface area (cm²); ^pBath pattern (dimensionless); ^qMode; ^rExposed skin area (cm²); ^sMinimum extreme.

significant differences ($p < .05$). These tests are based on the comparison of the medians of two or more independent non-normal subgroups (non-parametric tests). Their null hypothesis is that the means of the ranks of the k groups are not substantially different among them. Statistica 7.0 (Statsoft 2004) was used to run the tests.

Study of the input variables influence on the CR variance

To understand the contribution of each input variable to the CR variance a sensitivity analysis was performed. This was carried out using Crystal Ball 7.1 (Decisioneering 2007). This calculates sensitivity based on the rank correlation coefficients between every parameter of the model and the model's results while the simulation is running (Decisioneering 2007). This procedure was applied on data from the 5- and 20-year-old M and F groups, as representative cases of the studied groups.

Comparison among CR model input variables grouped by age and gender

To elucidate the causes of the divergence in the risk results between genders, we estimated gender differences for each input variable within the same age group by calculating the ratio among arithmetic means obtained using the Crystal Ball Scenario Analysis tool (Decisioneering 2007). This procedure identifies, based on MC resulting percentiles chosen by the operator, the corresponding trial values for each input variable, and then calculates its arithmetic mean by default. The chosen percentiles ranged from the 95th to the 100th. Significant differences were tested with Mann-Whitney.

Comparison between the main results of the present work and those of the prior study

Prior to the comparison of the results of both studies (*i.e.*, the results of the current one and those of Peluso *et al.* 2012), we calculated the difference between CRs computed with the 1D MC and 2D MC methods for the 5-year-old group data obtained in the previous study. That difference corresponded to the percent change in the 95th percentiles between the 1D and the 2D CR PDFs (using *Tevent*+*EF*+*Conc* as outer variables).

For the comparison of the results of both studies a method similar to the cross validation technique was applied. This "one-at-a-time perturbation technique" consisted in calculating the CR simply by sequentially exchanging *Ir*, *Tevent* and *EF* estimations from the prior study with those corresponding to the present study and analyzing the ratio change on the original 95th percentile of the 1D CR PDF as shown in Eq. (5):

$$CH\%n = (CR Pn\ dose - CR\ dose) / CR\ dose * 100 \quad (5)$$

where $CH\%n$ is the percent change in the prior study CR dose compared to the perturbed one by applying the cross validation technique; $CR Pn\ dose$ is the 95th percentile of the new PDF dose obtained after exchanging *Ir*, *Tevent* and *EF*, here represented by "n" $CR\ dose$ is the 95th percentile of the prior study 1D CR PDF dose.

The existence of significant differences was tested with Mann-Whitney. The analysis was applied to the 5-year-old group for the accidental water intake type of exposure because it was the most affected group according to the prior study.

Table 2. Comparison between M and F levels of uncertainty in CRs obtained using 1D and 2D MC for the 5-YO group exposed to As through accidental water intake.

	M				F			
	95th P	95th P 2D ^a	Diff. ^b	Sig. ^c	95th P	95th P 2D	Diff.	Sig.
1D	1.57E ⁻⁰⁵				1.06E ⁻⁰⁵			
2D <i>Ir</i>		1.47E ⁻⁰⁵	-6.01	No		9.75E ⁻⁰⁶	-8.32	No
2D <i>Tevent</i>		1.33E ⁻⁰⁵	-15.19	Yes		8.86E ⁻⁰⁶	-16.77	Yes
2D <i>EF</i>		1.32E ⁻⁰⁵	-15.57	Yes		8.39E ⁻⁰⁶	-21.18	Yes
2D <i>ED</i>		1.49E ⁻⁰⁵	-4.76	No		9.80E ⁻⁰⁶	-7.93	No
2D <i>Conc</i>		1.39E ⁻⁰⁵	-11.37	Yes		9.44E ⁻⁰⁶	-11.32	Yes
2D <i>Tevent+EF+Conc</i>		8.45E ⁻⁰⁶	-46.08	Yes		5.78E ⁻⁰⁶	-45.67	Yes

^aMean of the 500 95th percentiles from CR PDFs obtained by the 2D MC procedure.

^bPercent difference between 95th percentiles of the 1D and 2D CR PDFs using the variables in italics as outer 2D variables.

^cStatistical significance according to the non-parametric test of contrast of medians (alpha = 0.05).

Results

The estimated PDFs and statistical parameters for the CR input variables (*i.e.*, *Tevent*, *EF*, *BW*, *H*, *BSA*, *BP*, *ESA*) arranged by age and gender are presented in Table 1. The comparison among CR estimates from the 1D and 2D MC models is presented in Table 2. The application of the 2D MC model with one input exposure variable used at a time as an epistemic uncertainty variable showed that the three major contributors to the epistemic uncertainty were the bathing event duration (*Tevent*), the annual frequency of exposure (*EF*) and the As concentration (*Conc*). The application of the 2D MC model simultaneously considering *Tevent*, *EF*, and *Conc* as outer 2D variables, showed a reduction of more than 45% in the uncertainty levels for both genders. This can be evidenced in Table 2 when comparing the 95th percentiles or, graphically, comparing the CR cumulative PDFs in Figure 1. The 2D CR PDF curves for M and F were both shorter (and the 2D 95th percentiles were lower) than those of the 1D CR PDFs for M and F because each of the 2D 95th percentile is the mean of the 95th percentile values obtained by the 2D MC procedure rather than a true 95th percentile as in the case of the 1D MC. Thus, the 2D (*Tevent+EF+Conc*) was the model applied for the subsequent CR calculations.

The descriptive statistics of the 2D CR PDFs for accidental water intake, dermal contact and the aggregated exposure for each age and gender groups, are shown in Table 3. Only in a few cases the CR outcomes were larger—but slightly less than an order of magnitude—than the significance of the CR safe level ($10E^{-05}$), and only for the most conservative statistic (maximum value of CR PDF of 5-, 10-, and 15-year-old groups for accidental water intake and the aggregated exposure). This means that the CR values—represented by the 2D 95th percentiles—associated with bathing activities at Del Azul stream are within safe levels. The aggregated CR decreased with age and the accidental water intake was the main exposure route (from almost 80% to more than 95% when comparing the 2D 95th percentiles of CR PDF by accidental water intake and by aggregated exposure). Except in a few cases of dermal exposure (5-, 10-, and 15-year-old M), the 2D 95th percentiles differed significantly among age groups according to the Kruskal-Wallis test ($p < .05$).

Regarding gender differences in CR, in all age groups, except one case associated to the dermal exposure (*i.e.*, 10-year-old group), the CR values were significantly higher for M than for F within the same age group (Mann-Whitney, $p < .05$). This implies that the two

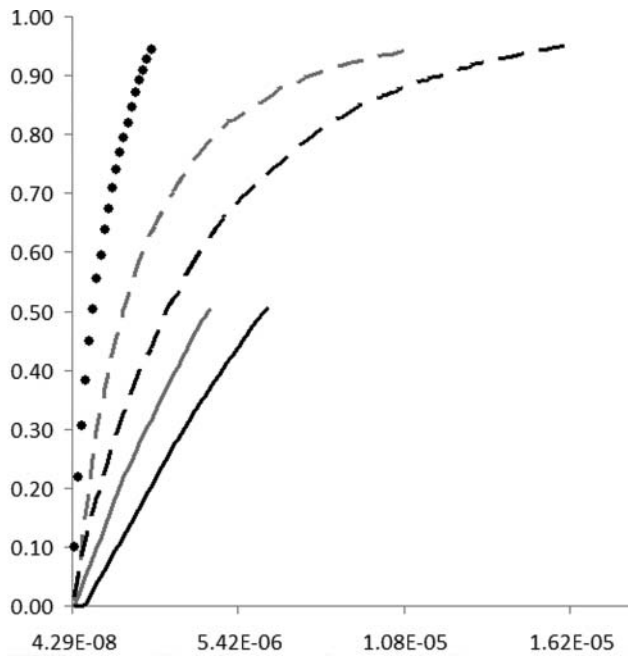


Figure 1. CR cumulative PDFs from 5-year-old M and F obtained with the 1D and 2D MC methods. References: black dotted line: Prior Study CR PDF; grey and black dashed lines: F and M 1D CR PDFs; grey and black solid lines: F and M 2D CR PDFs.

oldest groups had higher risk values than the two youngest ones for any of the three exposure routes. The 15-year-old group presented the highest divergence because the risk associated with the accidental water intake and with the aggregated exposure for M bathers was at least 270% higher compared to that for F. [Figure 1](#) evidences the gap in the 5-year-old 2D CR cumulative PDFs between M and F.

[Figure 2](#) shows the compared contribution of each input variable to the CR variance for accidental water intake measured as Spearman correlation coefficients. This test, performed on 5- and 20-year-old M and F, showed that the major contributors were *Tevent* and *EF*, both with Spearman coefficients higher than 0.5. *Tevent* and *EF* combined contributed to almost 70% of the total variance in both age groups. [Figure 2](#) also shows that there were slight differences in *EF* and *Tevent* between genders. Only the accidental water intake rate (*Ir*) showed significant differences between genders but its contribution to the total variance was minor. To enhance the analysis of gender differences in the input variables within age groups, we applied the scenario analysis and the results are presented in [Figure 3](#). *Ir* was the only input variable that differed significantly between genders in the 5- and 10-year-old groups according to the Mann-Whitney test ($p < .05$). *Tevent* and *EF*, the input variables with the most influence on CR variability according to the sensitive analysis, did not show differences between genders of the 5- and 10-year-old groups. However, differences for these variables were found between genders of the 15- and 20-year-old groups. This is because more input variables increased the difference between genders. For the 15- and the 20-year-old group three input variables were relevant: *Ir*, *Tevent*, and *EF* for the former age group and *Ir*, *Tevent*, and *BW* for the latter one. Because M in the 20-year-old group had a greater *BW* than F in the same age group, risk difference between genders was lower

Table 3. Descriptive statistics values for the 2D CR probability distributions grouped by age and gender for the three exposure routes and M to F 2D 95th percentile ratio.

Exp. pathway	Gender	Stat	5	10	15	20	
INT	M	AM 2D ^{a, b, c, d}	5.01E ⁻⁰⁶	3.18E ⁻⁰⁶	2.47E ⁻⁰⁶	5.48E ⁻⁰⁷	
		SD 2D ^{a, b, c, d}	2.01E ⁻⁰⁶	1.36E ⁻⁰⁶	1.06E ⁻⁰⁶	2.43E ⁻⁰⁷	
		95th P 2D	8.45E ⁻⁰⁶	5.57E ⁻⁰⁶	4.35E ⁻⁰⁶	9.84E ⁻⁰⁷	
		Min. 2D ^{a, b, c, d}	3.88E ⁻⁰⁷	2.30E ⁻⁰⁷	1.77E ⁻⁰⁷	3.69E ⁻⁰⁸	
		Max. 2D ^{a, b, c, d}	5.02E ⁻⁰⁵	4.52E ⁻⁰⁵	2.87E ⁻⁰⁵	1.12E ⁻⁰⁵	
		AM 2D	3.07E ⁻⁰⁶	2.36E ⁻⁰⁶	8.37E ⁻⁰⁷	2.45E ⁻⁰⁷	
	F	SD 2D	1.49E ⁻⁰⁶	1.16E ⁻⁰⁶	4.07E ⁻⁰⁷	1.28E ⁻⁰⁷	
		95th P 2D	5.78E ⁻⁰⁶	4.46E ⁻⁰⁶	1.58E ⁻⁰⁶	4.83E ⁻⁰⁷	
		Min. 2D	2.24E ⁻⁰⁹	9.76E ⁻⁰⁸	3.74E ⁻⁰⁸	4.55E ⁻⁰⁹	
		Max. 2D	5.67E ⁻⁰⁵	5.71E ⁻⁰⁵	1.52E ⁻⁰⁵	8.65E ⁻⁰⁶	
		M to F R ^e	146.00	125.88	275.95	203.73	
		Sig.	Yes	Yes	Yes	Yes	
	DERM	M	AM 2D	3.16E ⁻⁰⁷	3.07E ⁻⁰⁷	3.05E ⁻⁰⁷	8.58E ⁻⁰⁸
			SD 2D	1.23E ⁻⁰⁷	1.22E ⁻⁰⁷	1.21E ⁻⁰⁷	3.38E ⁻⁰⁸
95th P 2D			5.24E ⁻⁰⁷	5.14E ⁻⁰⁷	5.11E ⁻⁰⁷	1.43E ⁻⁰⁷	
Min. 2D			2.43E ⁻⁰⁸	2.21E ⁻⁰⁸	2.44E ⁻⁰⁸	6.35E ⁻⁰⁹	
Max. 2D			3.08E ⁻⁰⁶	5.94E ⁻⁰⁶	2.98E ⁻⁰⁶	1.46E ⁻⁰⁶	
AM 2D			2.62E ⁻⁰⁷	3.38E ⁻⁰⁷	1.71E ⁻⁰⁷	6.25E ⁻⁰⁸	
F		SD 2D	1.03E ⁻⁰⁷	1.35E ⁻⁰⁷	6.74E ⁻⁰⁸	2.54E ⁻⁰⁸	
		95th P 2D	4.37E ⁻⁰⁷	5.39E ⁻⁰⁷	2.85E ⁻⁰⁷	1.06E ⁻⁰⁷	
		Min. 2D	2.03E ⁻⁰⁸	2.63E ⁻⁰⁸	1.33E ⁻⁰⁸	3.01E ⁻⁰⁹	
		Max. 2D	5.36E ⁻⁰⁶	6.70E ⁻⁰⁶	3.12E ⁻⁰⁶	1.06E ⁻⁰⁶	
		M to F R	119.90	95.36	179.29	134.90	
		Sig.	Yes	No	Yes	Yes	
AGGR		M	AM 2D	5.14E ⁻⁰⁶	3.23E ⁻⁰⁶	2.74E ⁻⁰⁶	6.82E ⁻⁰⁷
			SD 2D	2.05E ⁻⁰⁶	1.37E ⁻⁰⁶	1.16E ⁻⁰⁶	2.95E ⁻⁰⁷
	95th P 2D		8.65E ⁻⁰⁶	5.73E ⁻⁰⁶	4.78E ⁻⁰⁶	1.21E ⁻⁰⁶	
	Min. 2D		4.07E ⁻⁰⁷	2.38E ⁻⁰⁷	2.07E ⁻⁰⁷	4.73E ⁻⁰⁸	
	Max. 2D		5.65E ⁻⁰⁵	3.87E ⁻⁰⁵	3.39E ⁻⁰⁵	1.30E ⁻⁰⁵	
	AM 2D		3.40E ⁻⁰⁶	2.81E ⁻⁰⁶	9.55E ⁻⁰⁷	3.29E ⁻⁰⁷	
	F	SD 2D	1.60E ⁻⁰⁶	1.35E ⁻⁰⁶	4.44E ⁻⁰⁷	1.61E ⁻⁰⁷	
		95th P 2D	6.31E ⁻⁰⁶	5.09E ⁻⁰⁶	1.76E ⁻⁰⁶	6.23E ⁻⁰⁷	
		Min. 2D	1.84E ⁻⁰⁷	1.60E ⁻⁰⁷	5.69E ⁻⁰⁸	1.64E ⁻⁰⁸	
		Max. 2D	5.58E ⁻⁰⁵	4.33E ⁻⁰⁵	1.91E ⁻⁰⁵	5.49E ⁻⁰⁶	
		M to F R	137.08	112.57	271.59	194.22	
		Sig.	Yes	Yes	Yes	Yes	

^{a, b, c, d}Mean of the 500 statistics values (for the mean, SD, min., and max.) of the PDFs obtained by the 2D MC procedure.

^eM to F 2D 95th percentile ratio.

Accidental water intake—INT; skin contact—DERM; aggregated exposure—AGGR.

in the 20-year-old than in the 15-year-old group. This is because *BW* is in the denominator position of the ADD equation and thus compensates the gender related differences between *Ir* and *Tevent*, which are in the numerator position. The arrangement of the mentioned input variables (*i.e.*, *Ir*, *EF*, *Tevent*, *BW*) in the ADD equation generates higher values for the 15-year-old than for the 20-year-old group. Briefly, M were found to be at a higher risk than F because of an increased accidental water intake during baths events, which are longer while age increases.

Regarding the analysis of the differences and similarities between the results of the current study and the previous one (Peluso *et al.* 2012), the trend of the results from both studies were coincident: none of the CRs were above the risk safe level, accidental water intake was the main exposure route, and CR scores according to age ranked as follows (in decreasing order): 5- > 10- > 15- > 20-year-old group. However, several differences between both studies can be pointed out. In Peluso *et al.* (2012) the 5-year-old group CR due to water

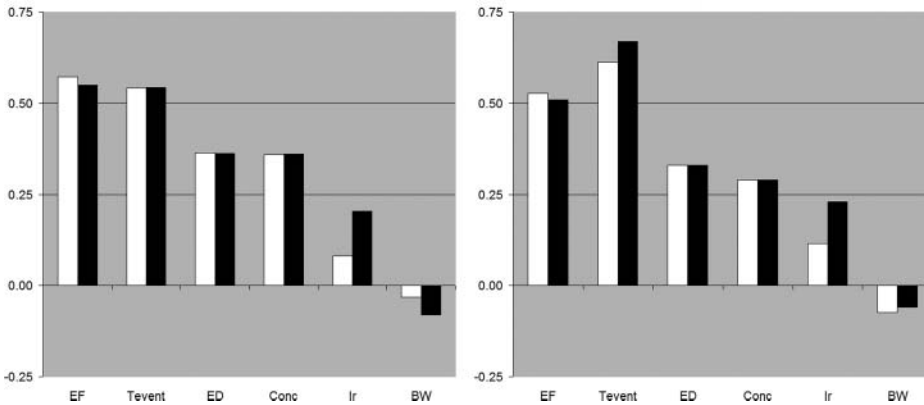


Figure 2. M (white bars) and F (black bars) exposure input variable contribution to CR variance due to accidental water intake in the 50- and 20-year-old groups (left and right graphs, respectively) measured by the Spearman correlation coefficients.

intake was $6.01E^{-06}$, an order of magnitude lower than the CRs for M and F of the 5-year-old estimated with the 1D MC method for the same exposure route. Nevertheless, that risk value was similar (same order of magnitude) to CR values estimated with the 2D MC method for M and F (Table 2). Considering only the 5-year-old group, Figure 4 presents the CR cumulative PDF from the prior study and the one for M and F from the current study, evidencing the differences among studies in contrast to the previous analysis, which considered only PDF statistics values.

Table 4 shows that if the 2D *Tevent*+*EF*+*Conc* methodology were applied on the prior study's data, the 2D 95th percentile CR value would have been 33% lower than in the previous study using the 1D MC method. That percentage would have been even lower than the one for the 1D/2D *Tevent*+*EF*+*Conc* relationship from this study (approximately a 45% difference, Table 2). In other words, the uncertainty of this study was higher than the one of the prior study. This could have been caused by (a) gender influence (not considered in the prior study) and update of the used data for the estimation of variables (*Tevent*, *EF*), (b) the change of *Ir* representation from a single value (50 mL h^{-1}) given by a deterministic model to the use of the whole *Ir* PDF (probabilistic approach).

Tevent and *EF* were higher in the present study than in the prior one. Although these differences were not so large when their statistics were compared (approximately a 2 to 4% difference for *Tevent* and a 6 to 8% difference for *EF* when comparing these input variables between studies), Figure 4 shows that the *EF* cumulative PDFs from both studies were clearly different whereas this did not happen for *Tevent*. Figure 4 also depicts that the deterministic value used for *Ir* in the previous study corresponds approximately to the 90th percentile in F *Ir* PDF but only to the 10th percentile in M *Ir* PDF. The effect of the differences in *Tevent*, *EF*, and *Ir* on CR between studies could be explained with the application of the cross validation technique, as presented in Table 4.

EF was the main input variable explaining the differences between both studies. Replacing the *EF* PDF in the ADD model of the prior study with the one for M of the current study caused a 40% increase in previous study CR. Similarly, when the *EF* PDF of the prior study

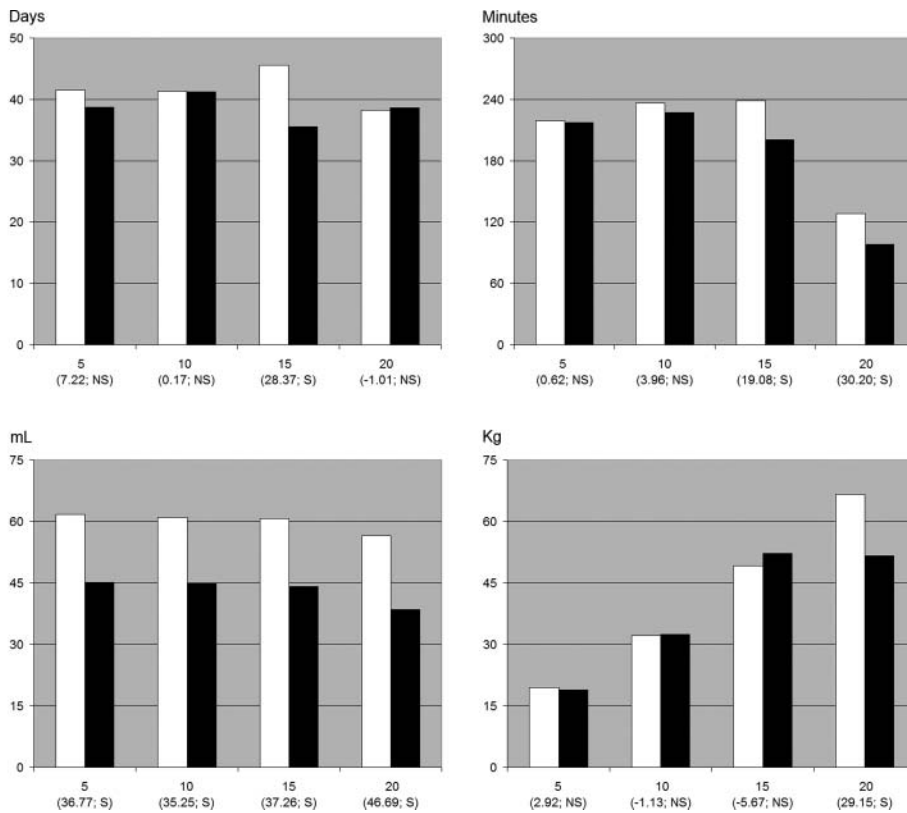


Figure 3. Scenario analysis for each of the 2D CR variables (*EF*, *Tevent*, *Ir*, *BW*, left to right and top to bottom graphs, respectively) in M (white bars) and F (black bars) of each age group (5-, 10-, 15-, and 20-year-old groups) exposed to As through accidental water intake. References: The number in brackets is the ratio between M and F mean values. S or NS indicates whether there is significance or not according to the Mann-Whitney test.

was replaced with the one for F of the current study, there was a 23% increase in previous study CR (lower than for M). This effect was not observed for *Tevent*, for which swapping values between studies did not cause a significant change in the results either using M or F PDFs.

When replacing the *Ir* deterministic value from the prior study with the M and F *Ir* PDFs from the current study, opposite effects on the CR results were observed. The use of M *Ir* PDF caused an 18% increase whereas the use of F *Ir* PDF caused a 20% decrease in the prior study CRs, respectively. The different effect caused by the use of M or F *Ir* PDFs can be attributed to the 90% of the F *Ir* PDF being below the deterministic value used in the prior study whereas 90% of the M *Ir* PDF was above that value.

Analysis and discussion

In environmental risk analysis, the improvement in the knowledge and understanding of the different types of uncertainty would aid in the decision-making process, as it is pointed out by Ascow II *et al.* (2008). As mentioned in a previous publication (Peluso *et al.* 2012), the

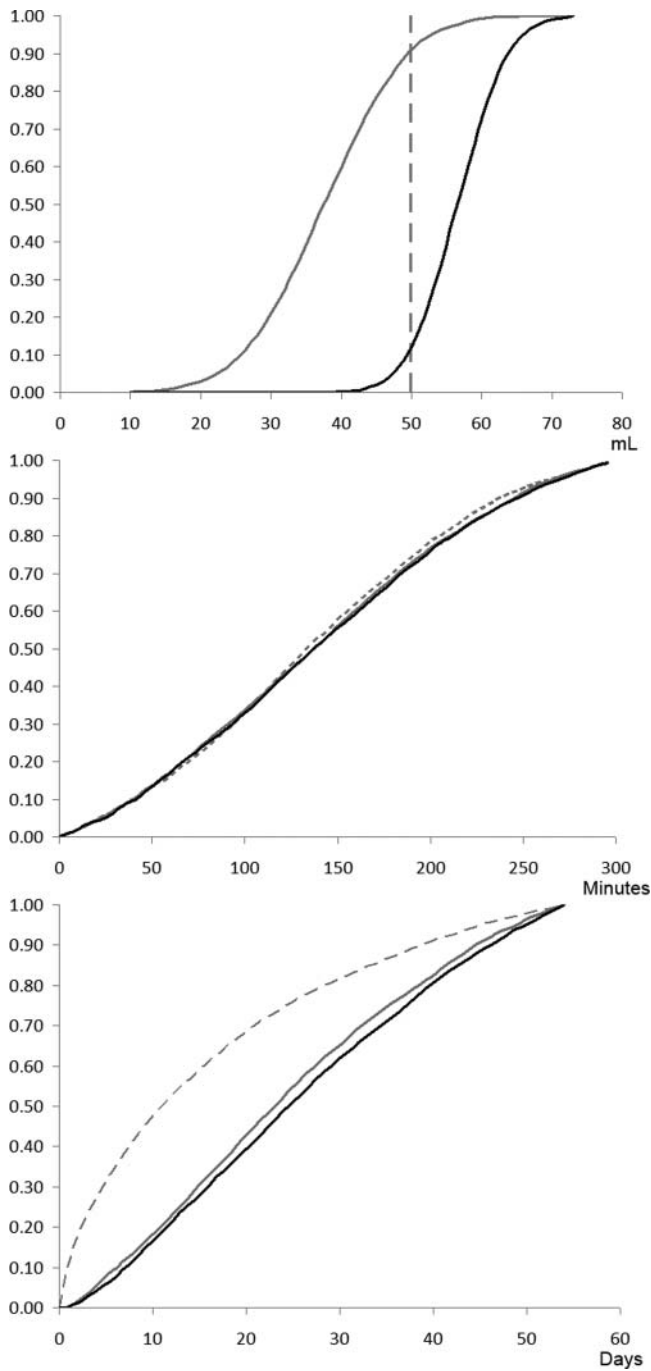


Figure 4. Comparison of I_r , T_{event} , and EF PDFs (top to bottom, respectively) between this study and the prior one, for the 5-year-old group. References: grey dotted line: Prior Study PDFs; grey and black solid lines: F and M PDFs obtained in the current study.

Table 4. Comparison between the CR values from the prior study (PS) obtained with 1D and 2D MC for the 5-year-old group exposed to As through accidental water intake (upper main row) and cross validation (CV) evaluation of the impact of the present study's *Ir*, *Tevent*, and *EF* PDFs on the prior study's model (lower main row).

		95th P	95th P 2D	Diff.	Sig.
1D vs. 2D PS	1D	6.01E ⁻⁰⁶			
	2D <i>Tevent</i> + <i>EF</i> + <i>Conc</i>		4.02E ⁻⁰⁶	-33.15 ^a	Yes
1D PS vs. 1D CV	1D <i>Ir</i>	7.09E ⁻⁰⁶		17.89 ^b	Yes
	1D <i>Tevent</i>	6.22E ⁻⁰⁶		3.50	No
	1D <i>EF</i>	8.38E ⁻⁰⁶		39.34	Yes

^aPercent difference in the 95th percentile values between 1D and the 2D CR PDFs using *Tevent*, *EF*, and *Conc* as outer 2D variables.

^bPercent difference in the 95th percentile values between original (PS) 1D and the "perturbed" 1D CR PDFs applying the present study's *Ir*, *Tevent*, and *EF* PDFs.

application of health risk assessment models for chemicals occurring in natural recreational waters used for bathing, swimming, wading, and so on has seldom been reported. Although some studies exist (e.g., Hussain *et al.* 1998; Albering *et al.* 1999; Baars 2002; Dor *et al.* 2003; Goldblum *et al.* 2006; Filipsson *et al.* 2009; Kumar and Xagorarakis 2010; Schets *et al.* 2011; Ollson *et al.* 2014), only Filipsson *et al.* (2009) of the above-cited examples quantified the impact of uncertainty as another component of the risk analysis.

In most risk assessment studies the uncertainty and variability of the input variables are frequently intentionally ignored (Carrington and Bolger 1998), for example, considering a hypothetical maximally exposed individual as representative of the population. Thus, the dose of exposure is estimated based on deterministic values, often applying conservative approaches using multiple safety factors (Lester *et al.* 2007). To perform a true population risk assessment, the variability of the exposure input variables (e.g., bodyweight, skin surface area, exposure duration, intake rate) should be considered because they could vary among individuals (Zhao and Kaluarachchi 2002).

To quantify the impact of uncertainty (epistemic and stochastic) on our study's results, we applied the probabilistic method that is the most frequently used (Darbra *et al.* 2007; Lester *et al.* 2007). Some examples of probabilistic HRA studies are: Schuhmacher *et al.* (2001); Ma (2002); Zhao and Kaluarachchi (2002); Glorennec (2006); Liao and Chiang (2006); Benekos *et al.* (2007); Lester *et al.* (2007); Filipsson *et al.* (2009, 2011); and Kumar and Xagorarakis (2010). However, the probabilistic method is criticized by some authors mainly due the dependency of sufficient data on the analyzed variables (Kentel and Aral 2007).

Although the 2D MC is a method that allows differentiating between epistemic uncertainty and variability with advantages over the 1D MC (USEPA 2001), the 2D MC weakness is that most environmental factors are both uncertain and variable (Lester *et al.* 2007). The comparison among CR PDFs estimated by 1D and 2D MC was done to choose which of the input variables should be considered as an outer 2D variable (epistemic uncertainty variable). However, some aspects related to epistemic and stochastic uncertainty of our study are discussed in the following paragraphs.

First and foremost, it should be noted that the USEPA HRA model is a screening method to quantify the health risk and it should be recognized that it is a very simplistic way of looking at the whole exposure process. In other words, the USEPA HRA model uncertainty is frequently not discussed. Nevertheless, USEPA HRA guidance is adopted for many state

environmental protection agencies in the United States (Lester *et al.* 2007) as well as in other countries. Most of the above-cited papers on HRA are based on the USEPA model.

This study was an attempt to know how the carcinogenic risk varies among age groups and genders. The differentiation among ages was made considering each age group independently of the others, as in Peluso *et al.* (2012). Another way of calculating risk could be to consider each age group as a discrete lifetime stage. This implies that for a certain age group the cumulative value from the previous age groups should also be taken into account. In other words, the 20-year-old age group risk should be the addition of the dose of exposure of the 5-, 10-, 15-, and 20-year-old groups. This valid approach for risk calculation requires the adjustment of the exposure variables but it does not allow the risk value comparison between age groups.

A methodological issue that must be discussed is the PDF model selection during the fitting process prior to the MC calculation. The input variable distribution selection is critical for any probabilistic model and “the selection process should preferably be based on observational data” (Sander *et al.* 2006, p 1364). However, when data are sparse or missing that selection is not precise (Sander *et al.* 2006). The literature indicates that a method for quantifying the uncertainty could be the MC application over different types of PDFs for each input variable; however, this approach is impractical (Sander *et al.* 2006). As previously stated, one of the three procedures for selecting the PDF model for some of the input variables was performed by applying the Anderson Darling goodness-of-fit statistic, which allowed us to select their best fit distribution. This procedure reduces the number of the possible PDFs to one, decreasing the subjectivity in the selection of the distribution. However, we are aware of another method that describes the probability distributions associated to input variables (*i.e.*, probability boxes), which could better account for uncertainty and variability when there are insufficient data (Sander *et al.* 2006; Filipsson *et al.* 2009). Since in our previous study (*i.e.*, Peluso *et al.* 2012) we used the method based on the Anderson Darling procedure, we replicated this same methodology in the current study for comparative purposes. In the future, we do not discard the possibility of considering the use of other methods, in particular the “probability boxes” as it was used in Filipsson *et al.* (2009), to account for the variability and uncertainty of the input variables.

Prior to the discussion about each input variable we must recognize that, although in this study we considered a larger sample size for several input variables than in our prior study, the completeness of the data is not enough to ignore the epistemic uncertainty in each variable. In this case, the variability and epistemic uncertainty are combined and difficult to separate (Sander *et al.* 2006), which tends to complicate the selection of the inner and outer variables during the 2D MC analysis. Data incompleteness could be a weakness of this study.

In the previous study the substances with the highest non-cancer and cancer risk scores were Cypermethrin and As, respectively (Peluso *et al.* 2012). We decided to carry out the present analysis based on As rather than Cypermethrin because As is not only the main carcinogenic substance according to the prior study but also its concentration in Del Azul stream waters is more stable than for Cypermethrin. Instead, Cypermethrin concentration in water is highly fluctuating (the coefficient of variation was higher than 540) due to episodic concentration peaks associated with pesticide applications in the basin. The regular As concentration (the coefficient of variation is 0.43) is explained by its natural occurrence in

the groundwaters of this region. The Del Azul stream basin is located in the Chaco-Pampean plain, an area with its groundwater source naturally contaminated with Arsenic and Fluoride (Nicolli *et al.* 2012). Due the close relationship between this stream and the groundwater aquifer (*i.e.*, during dry periods the stream persists due to the aquifer contribution) the stream waters have significant concentrations of As. As highlighted in our previous study, data on the concentration of harmful substances in Del Azul stream waters is scarce. Having more As concentration data could have had an effect on the probability distribution fitting, affecting the MC results. A deeper understanding of As concentration patterns in stream waters may help decide if As concentration can be excluded from the analysis as an outer 2D variable in future studies.

Another source of uncertainty with significant influence on risk results is the accidental water intake during the bath event. The change from a deterministic to probabilistic approach meant that we tried to address with this uncertainty. However, we assumed an Ir based on the literature (Dufour *et al.* 2006) rather than a local Ir . Despite we consider Ir as an inner variable during the 2D MC (only with stochastic uncertainty), we acknowledge that the use of surrogate information implies pieces of unquantified epistemic uncertainty.

Likewise, uncertainty could also be attributed to some input variables depending on bathers' perception ($Tevent$, EF) rather than on our direct observations. On the other hand, although the bath pattern (BP) type was based on behavioral observations of bathers, the selection of a triangular model PDF was assumed considering the three curve descriptors: minimum, maximum, and most likely.

In addition, for the dermal exposure estimation we did not consider the effect of having a wet bathing suit after exiting the water, which would increase the exposure time (until the swimming costume and body dry). The increase in the bathers sample size and a more comprehensive study on the bath practice (duration, daily frequency, percentage of body surface that is immersed and time length of immersion, average time it takes the swimwear and body to dry, *etc.*) should be carried out during future in situ studies.

As was previously indicated, in the absence of a local study, ED was based on the literature. This implies that in future studies this input variable should be subjected to observational testing under local conditions to reduce its uncertainty.

While the use of Argentine BW PDFs is an attempt to reduce uncertainty in comparison to the use of other source of information (*e.g.*, USEPA exposure factors), we recognize that it would have been more accurate to use the actual weights of the bathers but this procedure (*i.e.*, weighing people during in situ studies) resulted impractical for us. However, we considered BW as a stochastic variable during the 2D MC.

The toxicity of certain substances could be different depending on age and gender and these factors should be looked at during risk assessment (Falk-Filipsson *et al.* 2007). Besides the anthropometric differences among ages and between genders that may be of a greater or a lesser significance for the risk calculation (*e.g.*, body weight, height, body surface), the toxic response could also change because of physiological variations (*e.g.*, modes of action, toxicokinetics, toxicodynamics) due to age (Dourson *et al.* 2002; Hattis *et al.* 2003; Falk-Filipsson *et al.* 2007) and to gender differences (Gentry *et al.* 2003; Clewell *et al.* 2004; Falk-Filipsson *et al.* 2007). However, the USEPA does not make a distinction among ages or between genders when setting toxicological reference doses such as the RfD (non cancer risk reference dose) or the SF, which was considered in this study. This study applied a unique SF for all

age and genders following the USEPA protocol, which means that different physiological responses related to age and gender were not separately considered during risk estimation.

When we studied the CR due to recreational bathing considering the age factor, we found that the younger the bather the higher the risk. However, regarding gender differences we observed that what we expected (*i.e.*, that women would have been at higher risk than males) did not happen and that males were at higher risk than females. This is because certain of the studied variables related to the exposure (*i.e.*, accidental water intake rate, annual bath frequency and bath duration) have a greater impact on risk results than other (body weight). Furthermore, beyond the uncertainty of the input variables, this study was also able to demonstrate the importance of the simulation technique applied to the CR model (1D vs. 2D MC) and its impact on the results. It must be recognized that the results are highly dependent on the risk analysis technique applied.

Clearly, any methodological decision on exposure input variables or on the applied simulation technique has a significant influence on risk results and on their uncertainty. In consequence, the initial conditions for risk estimation should be thoroughly described to make the reader fully aware of the estimation procedure.

Finally, we want to highlight that, beyond the cited limitations, the set of tools utilized in this study (1D and 2D MC, rating of percentiles, sensitivity analysis, scenario analysis, and cross validation) is a powerful combo for improving the probabilistic health risk application.

Conclusions

None of the studied groups was at risk when considering CR due to As exposure during recreational bathing in waters of Del Azul stream. However, we observed significant differences in CR scores according to age, gender, and exposure route. The youngest age group (*i.e.*, 5-year-old) had the highest risk score associated with accidental water intake during bathing. In all the studied age groups, CR was higher in males than in females, with larger differences between genders for the two oldest age groups. The 15-year-old group showed the highest difference in the aggregated exposure risk between genders (270% difference, higher in M).

The spread of the risk results between genders responds primarily to the disparity in the accidental water intake due to bath duration (which resulted longer in M than in F). For the oldest groups the amount of ingested As increases because the duration of bathing events in males is longer in older than in younger groups.

The comparative analysis between the results of this study and those of our prior research highlights the importance of the analytical method and of the input variables used for risk estimation.

The health risk assessment applied to recreational waters of Del Azul stream allowed evaluating the water suitability for bathing according to age and gender and to understand what input variables mostly explained the results. The risk analysis tools, when properly implemented, would permit differentiating among diverse exposure scenarios, and they should always incorporate the study of uncertainty in their design, as it is promoted by the related literature.

Funding

This study was funded by the National University of the Center of the Buenos Aires Province (UNCPBA, Argentina), by the Scientific Research Commission of the Buenos Aires Province (CIC, Argentina), and the National Agency for Promotion of Science and Technology (ANPCyT PID 452, Argentina).

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