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[報 文]

A Probabilistic Risk Assessment for Inorganic Arsenic

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무기비소에 의한 확률론적 위해도 평가

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요 약 문

확률론적 해석방법은 환경독성물질에 의한 인체위해도 평가시 사용된 각 입력인자들의 불확실성까지 고려하는 방법론이다. 기존의 위해도평가방법론은 불확실성을 고려하지 않고 단순히 결과치의 포인트 값만을 제공하는데 비해 이러한 확률론적 해석방법은 입력인자들의 불확실성이 고려되고 결과치에 대한 이들의 중요도가 산출될 수 있는 등 더 많은 정보를 제공하므로써 환경위해도를 기반으로 한 환경정책 결정시 용이하게 사용될 수 있다. 본 논문은 현재 미국에서 음용수 기준설정시 논란이 많은 무기비소에 대해 확률론적 평가방법론을 적용하였다. 우선 인체위해도평가에 필요한 무기비소의 각종 자료들을 수집, 정리하고 이를 바탕으로 각 인자들의 불확실성을 파악하였다. 최종적으로 이들로부터 무기비소가 포함된 음용수를 마신 일반인의 피부암 위해도를 확률적으로 계산하였다. 또한 계산된 결과치와 여러 위해도기준치를 비교하여 정책결정에 필요한 의사결정에 대해서도 살펴보았다. 계산결과에 의하면 다수의 일반인들이 무기비소를 함유한 음용수섭취를 통해 현재 위해도설정치(10^{-6}) 보다 높은 피부암 위해를 입고 있는 것으로 나타나 이에 대한 규제가 필요하다고 본다.

INTRODUCTION

Arsenic is a ubiquitous element present in various compounds throughout the earth's crust. The use of arsenic compounds increased greatly during the 18th and 19th centuries, including its use in pigments and dyes, as a preservative of animal hides, in glass manufacture, agricultural pesticides, and various pharmaceutical substances. The causal association between human arsenic exposure, usually in the form of inorganic compounds containing trivalent arsenite (As^{III}) or pentavalent arsenate (As^{V}), and various forms of human cancer has been known for many years.[1] Especially, ingestion of inorganic arsenic has been known to cause a skin cancer. Recent epidemiological data also indicate that several internal cancers including lung, liver, bladder, and kidney are also caused by arsenic ingestion.[2] The National Interim Primary Drinking Water Regulation, promulgated under the Safe Drinking Water

Act, set the Maximum Contaminant Level (MCL) for inorganic arsenic in US public water supplies at 50 mg/L. In general, inorganic arsenic is not found in drinking water at levels exceeding this MCL in the USA.

Up to now, most human health risk assessments have used conservative "point" estimates (i.e., single values) to characterize the hazards associated with exposure to toxic chemicals in the environment. For example, a federal law in the USA requires the EPA (Environmental Protection Agency) to conduct site-specific risk assessments to support its selection of remedial actions for Superfund sites. The EPA procedures work by combining exposure estimates (specific to the site) with dose-response estimates (specific to each contaminant). The EPA's default exposure assumptions are a mixture of the best estimates (e.g., 70 kg body weight, 70 years of life) and upper bound estimates (e.g., 2 *L* of tap water ingested per day by an adult). The EPA calls this combination the "Reasonable Maximum Exposure" (RME), a protective case that is still within the range of possible exposures. Recent work done by Smith *et al.*[2] argues that, based on their point-estimate calculation results, measures to reduce arsenic levels in water supplies should be considered. This point-estimate approach usually does not lead to a realistic estimate of health risks, nor does it consider the uncertainty of output associated with the variation of input parameters. Hence, many risk analysists believe that characterizing estimated risks in terms of probable ranges, rather than as single point estimates, is the next best logical way to perform health risk assessments. This approach, called the "probabilistic" risk assessment, uses a distribution of data to represent key variables such as chemical concentrations, frequency, and body weight. This method can provide much useful information to risk managers. Although probabilistic analysis was rarely used in health risk assessment until 1989, this approach has recently been recognized as an important tool for the evaluation of health risks associated with hazardous waste and chemicals.

The study presents an assessment of the skin cancer risk from inorganic arsenic exposure through drinking water ingestion. The study uses a probabilistic risk assessment that has been recognized as an important tool in characterizing the health hazards associated with exposure to toxic chemicals in the environment. Compared to the current approach, which produces conservative estimates, this approach considers the uncertainty of its input values and evaluates realistic estimates of the health risks. Hence, the method provides useful information to the risk manager needing to make a wise decision regarding cancer risk associated with inorganic arsenic.

2. Cancer Risk Assessment for Inorganic Arsenic

1) Inorganic Arsenic

(1) Chemical Aspects

Arsenic (As), atomic number 33 and atomic weight 74.92, is a member of Group V of the periodic table of elements along with nitrogen, phosphorus, antimony, and bismuth. It occupies the position between phosphorus and antimony, and many of its physiochemical properties closely resemble those of phosphorus. It is classified as a metalloid, having chemical properties intermediate between typical metals and non-metals. Thus, arsenic is capable of forming alloys with metals but also readily forms covalent bonds with carbon, hydrogen, and oxygen. The chemistry of arsenic is rather complex, and the compounds it forms are numerous. This is largely because arsenic possesses several different valence or oxidation states, which result in the markedly different biologic behavior of its

compound. Arsine gas, containing the trivalent anion of arsenic (-3 oxidation state), is clearly the most toxic form of arsenic. Next are the commercially important trivalent arsenic compounds or arsenites in which arsenic is in its +3 oxidation state. Least toxic are the pentavalent or arsenate compounds, which contain arsenic in its +5 oxidation state. In general, inorganic arsenic compounds are more toxic than organic arsenic compounds of similar valency.

(2) Absorption

Arsenic may enter the body through the gastrointestinal tract, lungs, or skin surface.[3] The extent of absorption depends on both the chemical form of the arsenic compound and its physical state. Thus, less water-soluble compounds, such as As_2O_3, are poorly absorbed through mucous membranes compared to more water-soluble species, such as the arsenic salts.[3] In general, both trivalent and pentavalent inorganic arsenic compounds are well absorbed from the gastrointestinal tract. Organic arsenicals, on the other hand, are variably absorbed. Absorption of arsenic in the lungs is also dependent on chemical species and particle size.

(3) Distribution

Once in the bloodstream, arsenic initially becomes associated with the red blood cells, binding to the globin portion of hemoglobin. It does not readily penetrate the blood-brain barrier.[3] Redistribution is said to occurs within 24 hours, primarily to the liver, kidneys, spleen, lungs, and gastrointestinal tract. Minor concentrations may also be found in muscle and nervous tissue. Any arsenic remaining intravascularly becomes bound to plasma proteins. Characteristically, within 2 to 4 weeks of absorption, arsenic begins to be incorporated into hair, nails, and skin owing to its predilection for sulfhydryl groups, which are common in keratin. By 4 weeks, arsenic can be detected in bone, in which it substitutes for phosphate. It has been found that arsenic can readily cross the placenta and thus be transferred from the mother to the fetus.

(4) Biotransformation

The biotransformation of arsenic in humans *in vivo* is not completely understood. An extensive recent literature survey[1] demonstrates the *in vivo* methylation of inorganic arsenic to monomethylarsenic (MMA) and dimethylarsenic (DMA) in every mammalian system studied to date, including man. While the quantitative features of this phenomenon may vary among species, one can generally state that:

1) DMA is the major transformation product in both humans and animals, with the amount of MMA, when formed, being greater in humans, and

2) Methylation is assumed to be a route of detoxification, the methylated forms being not only much less toxic but also more rapidly excreted.

Another important observation[3] is that some reduction of pentavalent inorganic arsenic compounds to the trivalent might occur. Reduction of pentavalent arsenic in vivo is consistent with a reductive biomethylation mechanism, including initial reduction of pentavalent to trivalent arsenic prior to methylation.

(5) Excretion

The major route of arsenic elimination is through the kidneys. Small amounts may be also excreted in feces, bile, sweat, and breast milk. For a single oral dose, in several human studies4), around 60% of it was excreted within two days. Johnson and Farmer[5] found that continuous exposure to a small amount of arsenic resulted in the acquisition of a steady state. It is known that trivalent arsenic was excreted more slowly than an

equivalent dose of the pentavalent form, and higher doses of both forms were cleared relatively more slowly than lower doses.

2) Cancer Risk Assessment

Cancer risk assessment can be divided into four steps: hazard identification, dose-response analysis, exposure assessment, and risk characterization (See Fig. 1).

(1) Hazard Identification

The causal association between human arsenic exposure, usually in the form of inorganic compounds containing trivalent arsenite (As^{III}) or pentavalent arsenate (AsV), and various forms of human cancer has been known for many years.[1,2] Substantial evidence led the International Agency for Research on Cancer[6] to conclude that ingestion of inorganic arsenic can cause skin cancer. Also, recent epidemiological data indicate that several internal cancers are also caused by arsenic ingestion, including lung, liver, bladder, and kidney cancer.[2] Curiously, arsenic is the only known human carcinogen that does not demonstrate convincing carcinogenicity in animal bioassays.[1]

(2) Dose-Response Analysis

Based on the epidemiological data which involved a large population in the endemic area of Taiwan, a clear dose-response was observed. Using skin cancer prevalence rates from populations having different arsenic levels in their drinking water, the cancer potency factors have been derived based on the study by Tseng et al.[7]

(3) Exposure Assessment

Current intake of arsenic by U.S. adults comes from two paths: 1) from seafood, meat, poultry, grains and cereals and 2) from tap water. Although seafood and other food have high arsenic contents, most of it is the form of organic arsenic, which is much less toxic than inorganic arsenic. Hence, tap water would be the main source of inorganic arsenic.

(4) Health Risk Model

In order to estimate the risk associated with inorganic arsenic exposure through drin-

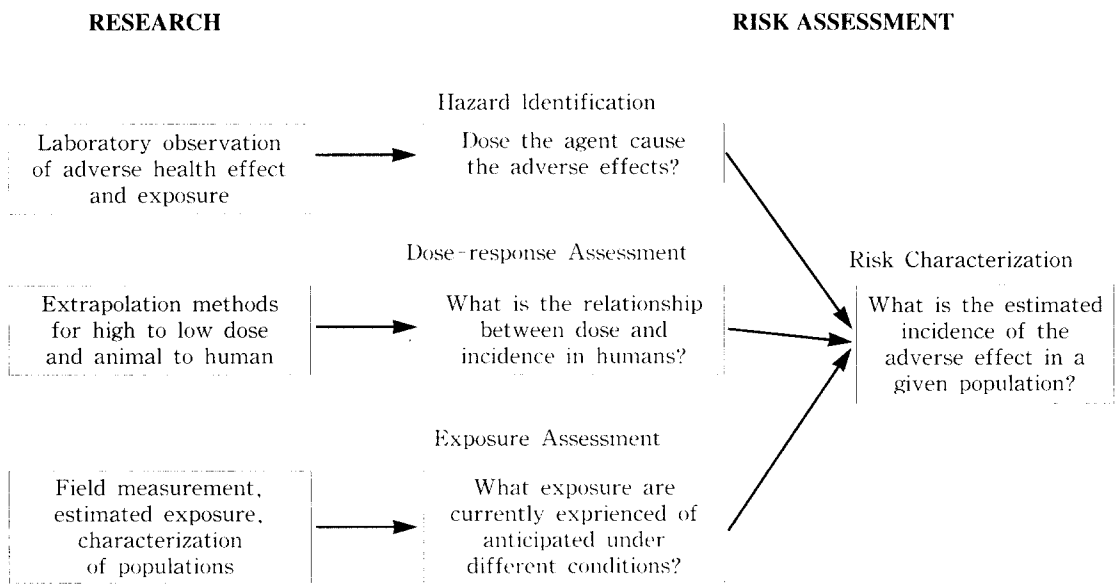

Fig. 1. Cancer Risk Assessment.

king water, the following equation is developed:

$$Risk=\frac{C_w*IR_W*EF*ED}{BW*AT}*CPF \quad (1)$$

where

C_w=contaminant concentration in drinking water (mg/L),

IR_W=drinking water ingestion rate (L/day),

EF=exposure frequency (days/year)

ED=exposure duration

BW=body weight of an exposed individual (kg)

AT=averaging time (25,550 days for carcinogens), and

CPF=cancer potency factor $(mg/kg/day)^{-1}$.

3. A PROBABILISTIC APPROACH

1) Method

Probabilistic analysis involves the determination of variation or uncertainty in an output function, based on the collective variation of model inputs (See Fig. 2). Hence, the analysis is sometimes called an "Uncertainty Analysis". For example, one can think of a model producing an output, y, such as a health risk, that is a function of several input variables, x_i:

$$y=f(x_1, x_2, x_3, \ldots, xn) \quad (2)$$

The variables, x_i, represent the various inputs to the risk assessment such as chemical concentration, exposure factor, cancer potency factor, etc. In the context of risk assessment models, uncertainty is used to describe (a) random variability in the parameters or measured data used in the models, and (b) the imprecision in the analysist's knowledge about models, their parameters, and/or their predictions. This study focuses on the uncertainty associated with variability, rather than imprecision. This uncertainty is due to actual, random behavior in some physically measurable quantity. Examples of the stochastic variability are variations in weather, variations in component failure times from one observation to another, and variations in consequences from one accident to another. Hence, this case assesses the uncertainty when the end point is an unknown distribution of values. The assessment end point is a true but unknown distribution of values representing random variability in the parameters or measured data used in the model.

Among the several methods for performing uncertainty analysis, the Monte-Carlo analysis is currently being widely used.[8] This method is based on performing multiple model evaluations using probabilistically selected model inputs, and then using the results of these evaluations to determine both the uncertainty in model predictions and the input variables that give rise to this uncertainty.

2) Quantification of Parameter Uncertainty

(1) Arsenic Levels in Drinking Water

The community Water Supply Survey conducted in 1969 found only 2 of the 969 supplies examined (0.2 percent) with levels exceeding 50 μg/L. The Rural Water Survey conducted in 1978 reported that 0.8 percent of rural households exceeded 50 μg/L. More recently, the EPA estimated that the inorganic arsenic level in the drinking water[9] of most public water supplies is below 5 μg/L and about 2,500,000 people drink water containing more than 25 μg/L of inorganic arsenic. While there is no accurate data on the average arsenic levels in drinking water, estimates range from 2.0 to 2.5 μg/L.

Based on these observations, this study uses the distribution of arsenic concentration in drinking water as a lognormal distribution with the median arsenic level of 2.5 μg/L and a 99 percentile value of 25 μg/L.

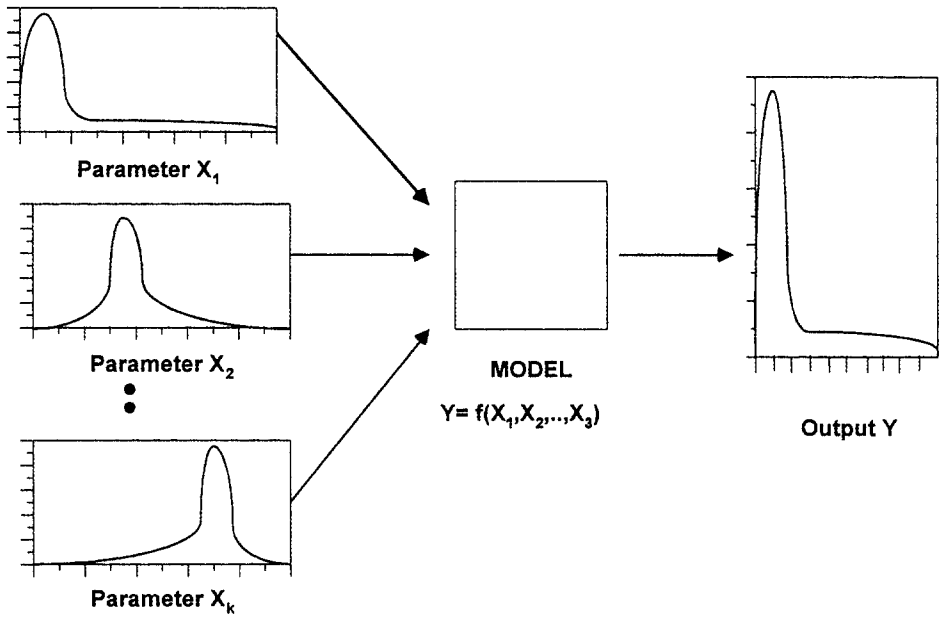

Fig. 2. A Schematic Diagram of Probabilistic Approach.

(2) Drinking Water Ingestion Rate

When estimating potential public health exposures and risks near hazardous waste sites, analysts often assume that adults ingest 2 liters of water per day. These standard assumptions, first published by the Safe Drinking Water Committee of the National Academy of Sciences in the United States, now appear in guidance manuals published by the USEPA for the "Superfund" and related programs. Recently, Ershow and Cantor[10] have published a statistical analysis of water intake rates for adults in different age groups. Roseberry and Burmaster[11] fitted lognormal distributions to the data. This paper uses the lognormal distribution for the analysis.

(3) Body Weight

The analysis takes lognormal distributions of body weight for men and women from Ref.[12]

(4) Cancer Potency Factor

This analysis has reviewed two carcinogenic potency factors: one from the 1984 EPA report[1] and the other from Brown.[13] Both utilize the skin cancer prevalence study by Tseng and colleagues.[7] The study consisted of 40,421 persons living in an area of Taiwan where there was known to be endemic arsenic contamination of the drinking water, and a control sample of 7500 essentially nonexposed individuals.

The 1984 EPA assessment, however, uses only the data for the males, for which the dose-response was stronger, and assumes that both Americans and Taiwanese consume the same volume of water per day (2 L/day). Also, it uses only those exposure/age groups in which skin cancer cases are present when deriving the dose-response model. The resultant values are controversially large. On the other hand, Brown's analysis used a maximum likelihood method to estimate a multistage-Weibull model with non-zero linear and quadratic coefficients of dose. It presented the value for both males and females. His calculations for lifetime risk of skin cancer

are 1.3/1000 for males and 0.6/1000 for females, per μg of arsenic per kg per day.

For the quantitative uncertainty analysis of inorganic arsenic, the analysis assumes that the variability in CPF can be represented by a lognormal distribution. At first, the analysis uses Brown's results as the medians of distribution for males and females, respectively. Since the CPF from the EPA study appears to be conservative and is derived only using the data for men, the analysis assumes the EPA value as the 95th percentile of the distribution for men. In order to obtain the distribution for women, the analysis assumes that the same error factor (the ratio between the median and the 95th percentile) derived from the distribution for men can be applied. In this case, the 95th percentile of CPF value for women can be calculated as 6.9 per μg of arsenic per kg per day.

(5) Other Parameters

The distributions of the other parameters can be seen in Table 1.

3) Calculations

Once the probability density functions (PDFs) of each input parameter in the models are defined, the next step is to use a suitable software to prepare the set of input variables based on a random sampling or LHS (Latin Hypercube Sampling) method. The, one computes a result from the model using these set of random variables,. This computation is repeated a large number of times to produce the complete distribution of the modeled variables. Finally, the distribution can be plotted and various statistical summaries of the results can be produced to help interpret the data. Because of the strong correlation of wate intake with body weight, the study uses the assumption that water

Table 1. Assumptions and Probability Density Functions (PDFs) used to Probabilistic Risk Estimates.

Parameter	Value in RME Analysis	Distribution Type	Distribution Parameters	Source
Arsenic Level (mg/L)	5.0×10^{-2}	Lognormal	GM=2.5×10^{-3} GSD=2.69	1),8)
Water Ingestion Rate (L/day)	2.0	Lognormal	GM=1.0 GSD=1.78	11)
Body Weight (kg)	70.0	Lognormal	Men: GM=76.6, GSD=1.19 Women: GM=64.68, GSD=1.22	12)
Exposure Duration (yrs)	24.0	Lognormal	GM=7.24 GSD=1.57	17)
Exposure Frequency (days/yr)	350.0	Triangular	min=180, best=345 max=365	17)
Cancer Potency Factor $(mg/kg/day)^{-1}$	1.3 (males) 0.6 (females)	Lognormal	Men: GM=1.3, GSD=4.4 Women: GM=0.6, GSD=5.04	

Note) RME: Reasonable Maximum Exposure
GM=Geometric Mean
GSD=Geometric Standard Deceviation
*: Estimated by the author

intake scales with body weight to the two-thirds power.[14] The other factors are assumed to be independent of each other in the analysis.

4) Results and Discussions

Table 2 shows the comparison of estimated skin cancer risk based on "Reasonable Maximum Exposure (RME)" analysis and probabilistic analysis for men and women. Results show that the RME point estimates are much greater than the 95th percentiles of risk calculated from probabilistic analysis. The results indicate that the average cancer risk is 2.18×10^{-5} and the 50th percentile is 3.54×10^{-5} for men. In this case, the plausible ranges for estimated skin risk (5th~95th percentiles) are 1.5×10^{-7} and 7.98×10^{-5}. For women, the average and median (50th percen-tile) cancer risk estimates are 1.16×10^{-5} and 1.94×10^{-6}. In this case, the 5th and 95th percentiles ranged from 8.09×10^{-8} to 4.43×10^{-5}. In order to examine whether or not an inorganic arsenic would pose a significant risk to a general population who uses tapwater as a source of drinking water, one should compare these estimated risks to the regulatory guideline for a "acceptable risk level". This study uses the USEPA guideline which established a typical "acceptable" risk level as 10^{-4} to 10^{-7} for Superfund sites.[15] Table 3 shows the percentage of a population which exceeds the criterion for both men and women. The decision making process in actual situation may not be an easy job since uncertainties in the domain should be considered. In such cases, the probabilistic analysis would provide a more realistic evaluation of skin cancer risk from inorganic arsenic intake considering the uncertainty of the input parameters.

Fig. 3 shows the complementary cumulative distribution function (CCDF) of estimated cancer risks for men and women. In this case, CCDF (R) is the probability that a value of R will be exceeded by a random value of estimated risk value. Based on these curves, the analysis predicts that approximately 74% of men and 53% of females in the general population exceed the cancer risk criterion when the 10^{-6} risk level (the USEPA's preferred risk goal) is selected. Based on these results, it appears that the current levels of inorganic arsenic in drinking water are likely to pose a significant risk to a population who uses tapwater as a source of drinking water. Hence, the study suggests that a measure to reduce inorganic arsenic levels in water supplies should be considered. Note that the results of the study are expected to be further improved if one employs more reasonable dis-

Table 2. Comparison of Risk Estimates Based On the RME and the Probabilistic Analysis.

Method	Lifetime Cancer Risk	
	Men	Women
RME Analysis	6.11×10^{-4}	2.82×10^{-4}
Probabilistic Analysis		
Mean	2.18×10^{-5}	1.16×10^{-5}
Percentiles		
5%	1.5×10^{-7}	8.09×10^{-8}
25%	9.55×10^{-7}	5.47×10^{-7}
50%	3.54×10^{-6}	1.94×10^{-6}
75%	1.33×10^{-5}	7.0×10^{-6}
95%	7.98×10^{-5}	4.431×10^{-5}

Table 3. Percentage of the General Population who Exceeds Each Risk Criterion Estimated by Probabilistic Analysis.

Risk Level	Men	Women
$>10^{-4}$	<0.1%	<0.1%
$>10^{-5}$	30%	20%
$>10^{-6}$ (The preferred risk goal by US EPA)	74%	53%
$>10^{-7}$	94%	90%

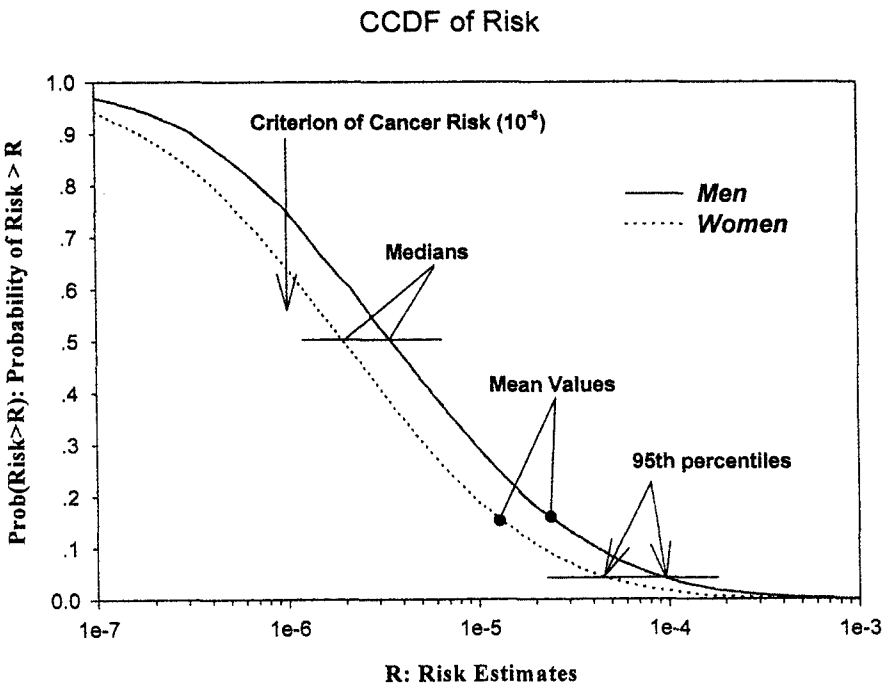

Fig. 3. CCDF for skin cancer risk estimates.

tributions of the parameters in the model.

SUMMARY

When one uses the conventional approach using conservative point-estimated values, results usually show the bounding estimates. This approach, however, does not lead to realistic estimates of health risks nor can it consider the uncertainty of its input values. In order to overcome these problems, this paper introduces the concept of probabilistic analysis. The probabilistic approach uses a distribution of key variables (chemical concentrations, frequency, and body weight, etc.) to represent their uncertainty. This method provides considerable useful information to the risk manager because it can identify the uncertainty of the results.

This paper has evaluated a probabilistic skin cancer risk associated with inorganic arsenic exposure by drinking water ingestion as the selected case study. Based on the results, the current level of inorganic arsenic in drinking water indicates that the majority of the general population exceeds the cancer risk criterion (10^{-6}) set by the EPA in the United States. Hence, it appears that measures to reduce arsenic levels in water supplies should be considered. The approach provides a more realistic evaluation of cancer from inorganic arsenic by considering the variation of its input parameters. Based on enough information from the analysis, risk managers would be able to make a wise decision regarding the cancer risk associated with inorganic arsenic.

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