Regulatory Toxicology and Pharmacology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The impact of recent advances in research on arsenic cancer risk assessment

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ARTICLE INFO

Article history:
Received 10 December 2012
Available online xxxx

Keywords:
Arsenic
Cancer risk
Non-linear
Adaptive
Dose–response

ABSTRACT

Scientific debate surrounds the regulatory approach for evaluating carcinogenic risk of arsenic compounds. The arsenic ambient water quality criteria (AWQC), based on the assumption of a linear mode of action for skin cancer risk, results in an allowable limit of 0.018 ppb in ambient waters; the drinking water Maximum Contaminant Level (MCL) was determined using a similar linear approach. Integration of results from recent studies investigating arsenic's mode of action provide the basis for a change in the approach for conducting an arsenic cancer risk assessment. Results provide support for a concentration demonstrating a dose-dependent transition in response from those representing adaptive changes to those that may be key events in the development of cancer endpoints. While additional information is needed, integration of current research results provides insight for a new quantitative cancer risk assessment methodology as an alternative toxicologically-based dose response (BBDR) cancer modeling. Integration of the new experimental results, combined with epidemiological evidence, support a dose-dependent transition concentration of approximately 0.1 μM arsenic. Some uncertainties remain; additional information from chronic *in vitro* studies underway is needed. Results to date also provide initial insight into variability in population response at low arsenic exposures.

1. Introduction

Over the last decade, there has been increasing scientific debate over the regulatory actions surrounding the determination of acceptable exposure concentrations for arsenic compounds. The debate centers around not only the selection of the most appropriate epidemiological data for dose–response assessment, but also the method that should be applied – mainly, a linear versus a non-linear approach. This continued debate has resulted in over a decade of regulatory conducted or commissioned assessments and reviews in an attempt to determine an acceptable oral concentration for population exposure to arsenic compounds.

In 2001, the Maximum Contaminant Level (MCL) for arsenic in drinking water was revised from 0.05 to 0.01 mg/L (USEPA, 2001). This value was derived based on the estimated dose–response based on risk distributions for bladder and lung cancer reported by Morales et al. (2000) in a population in Taiwan chronically exposed to concentrations of arsenic in drinking water as high as 1.75 mg/L. The dose–response calculations were performed under the standard regulatory default assumption of linearity, despite the growing scientific evidence at that time of a nonlinear mode of action for the carcinogenicity of arsenic (Abernathy et al., 1996; Clewell et al., 1999; Snow et al., 2001).

In its review of the underlying the basis for the MCL, the Science Advisory Board (SAB) of USEPA noted that the ultimate risk number derived from the Taiwanese study has proven very sensitive to the decision about the appropriateness of the comparison population, which had important implications for the use of the data to estimate risk in the United States (SAB, 2000). This comment was raised based on a study conducted in Utah (Lewis et al., 1999) that suggested that some U.S. populations may be less susceptible to the development of cancer than those in Taiwan. In addition, the SAB (2000) also agreed with a review by the National Research Council (NRC, 1999), that noted that the mechanisms associated with arsenic-induced cancer most likely have a sub linear character, which implies that linear models, such as those used by the Agency, overestimate risk.

In a subsequent reevaluation of the arsenic literature for purposes of the development of a recommended value for the

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http://dx.doi.org/10.1016/j.yrtph.2014.02.006
0273-2300/

Integrated Risk Information System (IRIS); USEPA (2005) again concluded that the mechanisms by which inorganic arsenic induces bladder cancer in humans are not yet known, but added that they are likely to be mediated by multiple modes of action. However, USEPA (2005) still relied upon a linear default approach for low dose extrapolation, because it lacked a full understanding of the arsenic modes of carcinogenic action. In a review of these analyses (SAB, 2007), the SAB agreed that available human and animal data do not fully describe the shape of the inorganic arsenic carcinogenic dose–response curve at low doses. The SAB also concluded that given the considerable uncertainties regarding low dose extrapolation, the SAB supported the use of a linear cancer risk model for inorganic arsenic as recommended by the NRC (2001) report. However, the SAB (2007) also recognized limitations to the Taiwanese data, and noted that there was evidence from inorganic arsenic animal toxicology, pharmacokinetics, and pharmacodynamics research, that suggested other than a linear bladder cancer dose–response. The SAB (2007) also made other recommendations, including the critical need for a continued research effort at that time to strengthen USEPA's cancer risk assessment for inorganic arsenic. The concerns and comments of the SAB (2007) were considered by the USEPA and in 2010 a new draft IRIS assessment was completed (USEPA, 2010). However, the 2010 IRIS draft was withdrawn by USEPA in early 2012.

In the current draft IRIS assessment (USEPA, 2010), an extensive database is provided on mode of action data that spans a three year period (2005–2007). However, there is no attempt to integrate the relevant information into the current dose–response assessment for inorganic arsenic. Although the dose–response assessment is based on epidemiological data even now resting principally on studies in one Taiwanese population, consideration of the wealth of information regarding mode of action in the determination of an acceptable exposure concentration is needed. In fact, this information is critical to insure that regulatory concentrations are not unnecessarily conservative.

In the decade that has passed since the USEPA (2001) assessment of inorganic arsenic, extensive research has been conducted that is focused on understanding the mode of action for the carcinogenicity of arsenic compounds (Boellmann et al., 2010; Chilakapati et al., 2010; Cohen et al., 2007; Suzuki et al., 2008, 2009, 2010; USEPA, 2010). While incorporation of mode of action data into a new paradigm for dose–response assessments is challenging, data relevant to the potential mode of action for the carcinogenicity of arsenic must be considered principally from a quantitative standpoint to best inform acceptable levels for human exposure. Consideration of mode of action data will require risk assessors and regulators to move beyond the standard paradigms to develop approaches that will allow consideration of expanding mode of action data to include genomics and modeling tools. USEPA (2010) recognizes this need and notes that "Due to the complexities of the possible mechanism of actions (MOAs) of inorganic–arsenic-mediated carcinogenesis, various scientific tools (e.g., genomic tools, human pharmacokinetic and biologically based dose response models) may be needed in order to interpret the data for the hypothesized key events qualitatively and quantitatively in a meaningful way."

In 2013, the National Academy of Sciences (NRC, 2013) provided an interim decision on the critical review of the USEPA (2010) draft IRIS assessment. In this review, the Committee noted that epidemiologic data are expected to serve as the basis for the dose response analyses for inorganic arsenic performed for most end points. Importantly, the Committee further noted that should the data in the range of observation be inadequate for developing risk estimates that meet EPA's needs, mode-of-action data should be used to the extent possible to extrapolate below the observed range. The Committee further commented on the importance of understanding interhuman variability and asserted that mode of action data can be used to guide modeling qualitatively in the low dose region and also in considering susceptibility even if the mode of action cannot be firmly established.

Recent research focused on understanding the potential changes in gene expression in the bladder tissue of both mice (Clewell et al., 2011) and humans (Yager et al., 2013) have provided insight into concentrations of arsenic associated with transitions in response, from potentially adaptive responses to those relevant for carcinogenicity. The integration of these data with other mode of action data and with results from the combined epidemiological data provide adequate quantitative information to justify a shift in the approach for conducting a cancer risk assessment for arsenic that is in contrast to the standard regulatory approach for this class of compounds. It also provides evidence of a concentration demonstrating a dose-dependent transition in responses from those representing adaptive change to those that may be key events in the development of cancer endpoints.

2. Evidence for an acceptable exposure concentrationfor arsenic compounds

The current regulatory approach for the determination of an acceptable exposure concentration for compounds typically involves a review of the peer-reviewed literature to identify the most sensitive cancer and/or noncancer endpoint in either animals or humans. The regulatory recommendations are typically based on the quantitative dose–response evaluation of a single study and a single endpoint (USEPA, 2012). In the case of arsenic compounds, the focus from a regulatory perspective has been largely on selected epidemiological studies from a population in Taiwan (Chen et al., 1985, 1988, 1992, 2004; Chiou et al., 2001; Morales et al., 2000). However, because of uncertainties typically associated with epidemiological studies, it is critical to consider toxicological data, such as mode of action data, in combination with epidemiological data in making regulatory decisions (Adami et al., 2011). These data can impact not only the method of dose–response modeling that is applied, but may inform the shape of the dose–response curve (linear versus nonlinear) and therefore, the potential for adverse effects in a population. In the case of arsenic compounds and the potential for bladder carcinogenicity, epidemiological, *in vivo* animal and *in vitro* studies are available that provide evidence that when integrated inform the shape of the dose–response curve for bladder cancer in the low concentration region Throughout the following sections, arsenic concentrations are expressed in the same units as stated in the original publication.[1]

2.1. Epidemiology studies

Several epidemiology studies provide quantitative information relevant for the evaluation of the potential risk of bladder cancer following arsenic exposure. Adequate exposure information is important to determine the potential concentrations at which effects may be observed. Studies that provide not only adequate exposure information, but also have ascertained exposure across a range of concentrations of necessity become the focus for consideration in a safety or risk assessment because adequate information is provided to evaluate the relationship between exposure or dose and the potential for adverse effects (Table 1). Taiwanese studies have historically served as the scientific basis for regulatory activity; however, studies undertaken in Europe and the U.S. are also available in which arsenic exposure, lifestyle and genetic

[1] To convert units: 1 μg/L = 1 part per billion (ppb); 1 μM iAs = 75 ppb, 1 part per million (ppm) = 1000 ppb.

Please cite this article in press as: Gentry, P.R., et al. The impact of recent advances in research on arsenic cancer risk assessment. Regul. Toxicol. Pharmacol. (2014), http://dx.doi.org/10.1016/j.yrtph.2014.02.006