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ABBREVIATIONS

BW – body weight

DMA – dimethylarsinate

DW – dry weight

EPA – US Environmental Protection Agency

FDA – US Food and Drug Administration

HPLC - high performance liquid chromatography

iAs – inorganic arsenic

ICPMS - inductively coupled plasma mass spectrometry

IR – intake rate

IRIS – EPA Integrated Risk Information System

LADD – lifetime average daily dose

MMA – monomethylarsonate

USDA – United States Department of Agriculture

WW – wet weight

ABSTRACT

Background: Arsenic-based drugs are permitted in poultry production. Inorganic arsenic (iAs) causes cancer and maybe other adverse health outcomes. The contribution of chicken consumption to iAs intake, however, is unknown.

Objectives: To characterize arsenic species profile in chicken meat and estimate bladder and lung cancer risk associated with consuming chicken produced with arsenic-based drugs.

Methods: Conventional, conventional antibiotic-free, and organic chicken samples were collected from grocery stores in ten US metropolitan areas from December 2010 to June 2011. 116 raw and 142 cooked samples were tested for total arsenic, and 78 samples $\geq 10\mu g/kg$ dry weight underwent speciation.

Results: Total arsenic geometric mean (GM) in cooked chicken meat samples was 3.0 µg/kg (95% CI: 2.5, 3.6). Among 78 cooked samples that were speciated, iAs concentrations were higher in conventional samples (GM = 1.8 µg/kg; 95% CI: 1.4, 2.3) than antibiotic-free (GM = 0.7 µg/kg; 95% CI: 0.5, 1.0) or organic (GM = 0.6 µg/kg; 95% CI: 0.5, 0.8) samples. Roxarsone was detected in 20 of 40 conventional samples, one of 13 antibiotic-free samples, and none of the 25 organic samples. iAs concentrations in roxarsone-positive samples (GM = 2.3 µg/kg; 95% CI: 1.7, 3.1) were significantly higher than in roxarsone-negative samples (GM = 0.8 µg/kg; 95% CI: 0.7, 1.0). Cooking increased iAs and decreased roxarsone concentrations. Compared to organic chicken consumers, we estimated that conventional chicken consumers would ingest an additional 0.11µg/day iAs (in an 82g serving). Assuming lifetime exposure and a proposed cancer slope factor of 25.7 $(\text{mg kgBW}^{-1} \text{ day}^{-1})^{-1}$, this could result in 3.7 extra lifetime bladder and lung cancer cases per 100,000 exposed-persons.

Conclusions: Conventional chicken meat had higher iAs concentrations than conventional antibiotic-free and organic chicken meat samples. Cessation of arsenical drug use could reduce exposure and the burden of arsenic-related disease in chicken consumers.

INTRODUCTION

Arsenic-based drugs have been used in poultry production for decades (Silbergeld and Nachman 2008). Roxarsone (3-nitro-4-hydroxyphenylarsonic acid) was approved in 1944 by the US Food and Drug Administration (FDA) to treat coccidiosis (a common parasitic disease in poultry), to improve feed conversion (which allows poultry to gain weight faster), and to improve meat pigmentation (Silbergeld and Nachman 2008). In 2010, industry representatives estimated that 88% of the roughly nine billion chickens (United States Department of Agriculture 2012b) raised for human consumption in the US received roxarsone (Nachman et al. 2012). Because of concerns regarding human arsenic exposure, the practice of administering roxarsone to poultry is under question (Maryland General Assembly 2012). Arsenic toxicity is species-dependent and is well established for inorganic arsenic (arsenite and arsenate). Chronic inorganic arsenic exposure causes lung, bladder and skin cancers (International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans 2012) and has been associated with multiple non-cancer health outcomes, including cardiovascular disease (Chen et al. 2011; Medrano et al. 2010; Sohel et al. 2009), type 2 diabetes (Navas-Acien et al. 2008), cognitive deficits (Wasserman et al. 2007), and adverse pregnancy outcomes (Ahmad et al. 2001).

Little is known about poultry metabolism of roxarsone. A small number of studies have examined total arsenic concentrations in the tissues of chickens that received roxarsone (Morrison 1969) or were assumed to have been administered the drug (Lasky et al. 2004; Wallinga 2006) (Table 1). In addition, a study by the FDA reported increased concentrations of inorganic arsenic in chicken livers associated with roxarsone supplementation (Food and Drug

Administration 2011b). To minimize arsenic accumulation in the edible tissues of the bird, FDA requires a five day drug withdrawal period for roxarsone prior to slaughter (Food and Drug Administration 2012b). To our knowledge, arsenic species have never been characterized in the muscle tissue of roxarsone-treated chickens. In July 2011, in response to an FDA safety evaluation, the leading manufacturer of roxarsone suspended sales in the US. Marketing of roxarsone, however, has continued in other countries, and the manufacturer has noted that the decision to suspend roxarsone sales in the US is under internal review (Harris and Grady 2011).

Information on the inorganic arsenic content of poultry meat is needed to quantify the public health burden associated with the use of arsenic-based drugs in poultry production. We conducted a market-basket study of chicken meat products in the US to estimate exposures to inorganic arsenic and other arsenic species resulting from chicken consumption. As a secondary objective, we estimated cancer risks associated with consumption of chicken produced with arsenic-based drugs.

METHODS

Sample Collection

From December 2010 to June 2011 (prior to the suspension of marketing of roxarsone), we purchased chicken breasts from 10 geographically diverse metropolitan areas across the US (Table 2). Between 5-10 grocery stores were visited for chicken purchases in each metropolitan area. No more than a single package of any brand of chicken was purchased from the same store, though multiple brands of chicken were purchased from the same store. We analyzed 142 chicken breast samples for total arsenic concentrations, representing 60 unique chicken brands acquired from 82 stores (47 supermarket chains). Of collected chicken samples, 69 were

conventional, 34 were conventional antibiotic-free, and 37 were USDA Organic (hereafter referred to as "organic"). In each city, we collected between 6-9 conventional chicken packages, 2-5 organic packages, and 2-6 conventional antibiotic-free packages, except in Baltimore, where no packages of conventional antibiotic-free chicken were purchased. Due to budgetary constraints, arsenic species concentrations were only measured in chicken samples with dry weight (DW) total arsenic concentrations ≥ 10 μg kg^{-1} resulting in a total of 78 samples with arsenic speciation, including 40 conventional, 13 conventional antibiotic-free and 25 organic samples.

Chicken samples were packed into coolers and shipped overnight by commercial carrier to Johns Hopkins University in Baltimore, MD. Upon receipt, chicken packages were stored at -20 ˚C until sample preparation.

Sample Preparation

For raw chicken, a single thawed breast was removed from each package and sliced lengthwise into halves to create paired samples. One half of each breast was processed raw, and the other half was baked in a household kitchen oven (set at 177 ˚C) to an internal temperature of 75 ˚C (United States Department of Agriculture 2012a), cooled, and stored frozen prior to processing. Individual raw and baked samples were homogenized separately in a blender with the addition of 50 to 100 mL MilliQ water (Millipore Corporation, Billerica, US) to aid blending. Blended samples were stored in sealable bags at -80 ˚C. The food processor and all laboratory equipment were cleaned between samples with hot water, soaked for 30 min in a 10% nitric acid bath, and rinsed with MilliQ water.

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Homogenized chicken meat samples were freeze-dried using a Freezone 2.5 freeze dryer (Labconco, Kansas City, US), and stored as a crumbled powder in 50 mL polypropylene tubes at 25 °C. Sample weights were recorded before and after freeze-drying. Samples were shipped to the Institute of Chemistry-Analytical Chemistry, Karl Franzens University Graz, Austria for arsenic analyses. Samples were analyzed in a random order, and the laboratory was blinded to the type of sample (cooked vs. raw) and to paired samples.

Arsenic Analyses

Detailed information on laboratory methods used to measure arsenic concentrations are provided in Supplemental Material. In brief, total arsenic concentrations in freeze-dried chicken meat samples were determined by inductively coupled plasma mass spectrometry (ICPMS) (Agilent 7500ce, Agilent Technologies, Waldbronn, Germany), following microwave-assisted acid digestion. For samples with DW total arsenic concentrations ≥ 10 μg kg^{-1} (N=78), arsenic species were measured using high performance liquid chromatography (HPLC; Agilent 1100) coupled with ICPMS which served as the arsenic selective detector. The method allowed for the quantitative determination of inorganic arsenic (arsenate and arsenite), dimethylarsinate (DMA), monomethylarsonate (MMA), and roxarsone. Another unknown arsenic species, perhaps a roxarsone metabolite, was also quantified in some samples that had positive roxarsone detections (31 samples of 49 positive for roxarsone). Two samples had significant amounts of arsenic eluting at the void volume of the HPLC column.. This was presumed to be arsenobetaine, possibly as a result of chickens being fed fishmeal (Food and Agriculture Organization 2012). Other unknown arsenic species were occasionally also present in some of the samples, but usually at trace levels. The limit of detection was 1 μg kg^{-1} DW for total arsenic, inorganic arsenic, DMA and MMA and 2 μg kg^{-1} DW for roxarsone. Total arsenic was detected in all

samples. Inorganic arsenic, DMA, roxarsone and the unknown arsenic species were detected in 100%, 99%, 27% and 22% of the speciated samples, respectively. MMA was detected in 36% of samples, but the concentrations were low and above the quantitation limit only for 23 samples (data not shown). Given the low MMA concentrations, it was dropped from further analyses. For other species, samples below the limit of detection were imputed as the corresponding detection limit divided by the square root of two.

Since arsenic measurements were performed on freeze-dried samples, it was necessary to account for moisture lost during the drying process when estimating concentrations in edible meat. Sample-specific water loss dilution factors were calculated by dividing the DW sample mass by the wet weight (WW) mass less the added Milli-Q water. Then, we multiplied the DW arsenic concentration by its sample-specific water loss dilution factor to produce a WW arsenic concentration.

The reference material SRM 1568a Rice flour (National Institute of Standards and Technology, Gaithersburg, US) was used to validate the method for total arsenic measurements. Subsequently, two in-house reference materials (rice and "low arsenic chicken breast") were prepared and analyzed in quadruplicate with each batch of samples as quality control. For speciation analyses, stock solutions containing 1000 mg $As \cdot L^{-1}$ each of the following species were prepared in water or 1% aqueous ammonia solution (for roxarsone): arsenite and arsenate prepared from $NaAsO_2$ and $Na_2HAsO_4 \cdot 7H_2O$, respectively (Merck, Darmstadt, Germany); MMA prepared in-house from As_2O_3 and CH_3I (Meyer reaction); DMA prepared from sodium DMA (Fluka, Buchs, Switzerland); and roxarsone (grade Vetranal) purchased from Sigma Aldrich (Vienna, Austria). Chromatograms for the standards and representative samples are provided in Supplemental Material, Figures S1 and S2.

There is currently no chicken meat reference material certified for total arsenic content. The method was validated against SRM 1568a Rice flour with a certified arsenic content of 0.29 ± 0.03 µg arsenic g^{-1}; we obtained 0.31 ± 0.01 µg arsenic g-1 (mean $\pm$ SD, n=16). At the time of validating the method with the SRM 1568a rice flour, we analyzed an in-house rice reference material obtaining a reference arsenic value of 257 ± 9 µg arsenic·kg^{-1} (n=105). This in-house rice reference material was subsequently used for day-to-day quality control; it was analyzed with all batches of samples over the course of the study, giving the following results: 252 ± 7 µg arsenic kg^{-1} (inter-assay coefficient of variation 2.9%, n=34, excluding a single outlier with 285.2 µg arsenic g^{-1}). Additionally, a sample of "low arsenic chicken breast" was prepared and similarly analyzed over the course of the study giving a mean value of 13.67 ± 0.99 µg arsenic g^{-1} (inter-assay coefficient of variation 7.3%, n=35, excluding a single outlier with 19.1 µg arsenic g^{-1}). The duplicate analysis of the chicken samples on two separate days (i.e. n=4 in total) served as a check for outliers: throughout the study (258 samples, 1032 measurements) 6 outlier measurements were identified in which case the sample was either re-measured or the outlier was excluded and n=3 was used for those samples. Thus, each chicken breast sample result is the mean of four sub-samples (or three in the case of an excluded outlier).

Ten samples were analyzed as lab-blinded duplicates to assess the quality of the testing and laboratory analysis. Relative percent differences (RPD) were determined for the concentrations of total arsenic and all analyzed species among the ten pairs of samples and duplicates. The RPDs for total arsenic, inorganic arsenic, DMA, roxarsone, and the unknown species were 1.9 %, 12.6 %, 1.1 %, 7.3 % and 15.8 %, respectively.

Analytical considerations

Although there have been several studies dealing with the use of roxarsone in the poultry industry, most of them have used anion-exchange HPLC-ICPMS to investigate the fate of arsenicals in poultry waste (Garbarino et al. 2003; Jackson and Bertsch 2001), and there have been few studies investigating roxarsone in chicken meat. Dean et al (1994) did not detect roxarsone (limit of quantification 0.25 ng arsenic g-1) in chickens fed on a roxarsone-supplemented diet with or without a withdrawal period (Dean et al. 1994), and Sánchez-Rodas et al. (2006) found nitarsone but not roxarsone in commercially available chicken breasts (Sánchez-Rodas et al. 2006).

To test our starting hypothesis - that chickens fed roxarsone would have elevated levels of inorganic arsenic – we developed an analytical method, comprising both an extraction step and HPLC, that could determine both inorganic arsenic and roxarsone. We had previously shown that acidic solutions suitable for extracting inorganic arsenic from foodstuffs (Raber et al. 2012) were not suitable for roxarsone (Nachman et al. 2012). Concurrent with our attempts to find the most suitable extraction conditions, we explored HPLC conditions appropriate for inorganic arsenic and roxarsone, and found that an anion-exchange column (PRP-X100) and a mobile phase of 20 mM malonate pH 9.5 gave good retention and separation of DMA, MMA, inorganic arsenic, and roxarsone. To simplify the arsenic speciation analysis, we tested the extraction of arsenic from chicken breast with extraction mixtures based on the HPLC mobile phase, and found that a solution of 20 mM malonic acid at pH 9.5 containing 1 % of a 30 % hydrogen peroxide (10 mL added to 500 mg freeze-dried chicken; mixture heated in a shaking water bath at 50 ºC for 1 hour) effected essentially quantitative extraction of arsenic from the chicken samples.

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Other variables

Chicken samples were categorized by package label into three groups: organic, conventional, and conventional antibiotic-free. Under the USDA Organic certification program, organic chickens are not permitted to be administered arsenic-based drugs. Conventional producers are not obligated to report arsenical drug use on package labels, and the "antibiotic-free" label does not preclude the use of arsenic-based drugs from a regulatory standpoint. Consequently, we used producer websites, emails and phone correspondence to determine whether companies have arsenical drug use policies. This information was used to categorize samples into a second scheme, consisting of conventional samples with (N=59) and without (N=46) stated policies prohibiting arsenical use. Speciated samples were also categorized *a posteriori* based on the presence/absence of roxarsone.

Statistical Analyses

Statistical analyses were performed with Stata 11 (College Station, TX, US). Geometric mean arsenic concentrations and 95 % CIs were calculated to evaluate differences among categories of chicken samples, between samples with and without roxarsone detections, and among metropolitan areas where samples were collected. To analyze differences between matched cooked and raw samples, paired t-tests were performed on log-transformed arsenic data. Non-parametric Spearman's correlation coefficients were used to assess relationships between concentrations of total arsenic and arsenic species. Statistical significance was two-tailed and set at $\alpha=0.05$.

Risk Analysis

To estimate the increase in population cancer risks associated with use of arsenical drugs in poultry production, we calculated the difference in geometric mean inorganic arsenic

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concentrations between the categories of chicken products (by package label, by arsenical drug use policy, and by positive roxarsone detection). These differences were then used to estimate lifetime average daily dose (LADD) of inorganic arsenic using the formula:

$$LADD = ([iAs] \times IR) / BW, \qquad [1]$$

where LADD= lifetime average daily dose (in mg $kgBW^{-1}$ day^{-1}), [iAs] = difference in inorganic arsenic concentrations between sample categories (in mg kg^{-1}), IR = per capita poultry intake rate (0.0824 kg day^{-1}) (United States Environmental Protection Agency 2011b), and BW = body weight (80 kgBW) (United States Environmental Protection Agency 2011a).

Cancer risk in chicken eaters was estimated by multiplying the LADD by the Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) cancer slope factor (q*) for inorganic arsenic:

$$Risk = LADD \times q* \qquad [2]$$

The current cancer slope factor in the EPA IRIS database for inorganic arsenic was last revised in 1998 and listed as 1.5 [mg $kgBW^{-1}$ $day^{-1}]^{-1}$, corresponding to skin cancer (United States Environmental Protection Agency 2013). The cancer potency of inorganic arsenic is currently being reassessed by the IRIS program, however, and in an external peer review draft of the document, a cancer slope factor of 25.7 [mg $kgBW^{-1}$ $day^{-1}]^{-1}$ is proposed, corresponding to cancers of the bladder and lung (United States Environmental Protection Agency 2010). This new cancer slope factor, derived from a 2010 analysis of the epidemiologic literature, was used in the risk analysis.

The 70-year lifetime population burden was calculated by multiplying the estimated risk by the size of the population at risk. Specifically, we assumed that 75% of the US population consumes

chicken based on nationally-representative data on the quantity and frequency of chicken consumption from the National Health and Nutrition Examination Survey (United States Environmental Protection Agency 2011b), and used 2011 Census data to determine the US population size (311,591,917) (United States Census Bureau 2012).

RESULTS

Arsenic species in chicken meat

The geometric mean (GM) for total arsenic was 3.0 µg kg^{-1} (95% CI: 2.5, 3.6) in cooked chicken meat samples (Table 2) and 2.4 µg kg^{-1} (95% CI: 2.0, 3.0) in raw samples (Supplemental Material, Table S1). The increase in total arsenic concentrations observed in cooked samples is likely due to loss of moisture during the cooking process. Among samples with arsenic speciation (cooked N=78 and raw N=65), the geometric means for inorganic arsenic, DMA and roxarsone were 1.1 µg kg^{-1} (95% CI: 0.9, 1.3), 3.5 µg kg^{-1} (95% CI: 3.1, 4.0) and 0.6 µg kg^{-1} (95% CI: 0.5, 0.7), respectively, for cooked samples and 0.7 µg kg^{-1} (95% CI: 0.6, 0.9), 2.7 µg kg^{-1} (95% CI: 2.4, 3.1) and 0.7 µg kg^{-1} (95% CI: 0.6, 0.9), respectively, for raw samples. Cooked meat concentrations of inorganic arsenic in conventional chicken samples were significantly higher than conventional antibiotic-free samples and organic samples (Table 2). When conventional samples were classified according to arsenic drug-use policies, differences in inorganic arsenic concentrations between groups were more apparent. The geometric mean inorganic arsenic concentration for companies who had policies against arsenical drug use (GM = 0.7 µg kg^{-1}; 95% CI: 0.5, 0.9) was significantly lower (p= 0.0004) than that for companies with no known policy (GM = 2.0 µg kg^{-1}; 95% CI: 1.6, 2.5).

Among cooked samples, roxarsone was detected in 19 of the 40 conventional samples and in 20 of 34 samples from producers without arsenical drug prohibition policies, compared to none of the 25 organic samples, and only 1 of the 13 conventional antibiotic-free samples (from a producer with a stated prohibiting policy).

Roxarsone was detected in cooked chicken samples from all cities except New York, San Francisco, and Seattle, and unknown species were detected in samples from 5 of the 10 metropolitan areas (Table 2). In raw samples, roxarsone was detected in samples from all cities except Seattle, and the unknown species was detected in samples from all cities except San Francisco and Seattle (Supplemental Material, Table S1). Some differences in total arsenic, inorganic arsenic or DMA concentrations were observed across metropolitan areas for cooked and raw samples. Cooked samples for total arsenic were higher in Flagstaff, AZ than in both New York, NY (p=0.001) and Seattle, WA (p=0.042). Inorganic arsenic concentrations in cooked samples from Baltimore, MD were higher than those in Seattle, WA (p=0.04). Among raw samples, significant differences in total arsenic levels were observed between the samples from Baltimore, MD and both Seattle, WA (p = 0.048) and New York, NY (p=0.044). DMA concentrations were significantly higher in cooked chicken from New York as compared to Fayetteville (p = 0.02).

Correlation among arsenic species

In both raw and cooked samples, moderate to strong correlations were observed between inorganic arsenic, roxarsone, and the unknown arsenic species, whereas correlations of these arsenic species with DMA were relatively weak (coefficients ranging from 0.11–0.36) (Table 3). The weak correlation between roxarsone and DMA (0.17 and 0.25 for raw and cooked samples, respectively) suggests that there may be little or no metabolic conversion of roxarsone to DMA

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within the chicken. The strong correlation of roxarsone with inorganic arsenic (0.75 and 0.68) and the unknown arsenic species (0.63 and 0.52) in chicken meat suggests that at least some of those species could be roxarsone metabolites.

Yao et al. recently reported inorganic arsenic contamination of commercial roxarsone formulations (Yao et al. 2012). An earlier study by Pizarro et al. (2004) that examined drinking water arsenate exposure and the resulting biotransformation and distribution of arsenic species in chicken cardiac muscle and meat tissues suggested that chickens are capable of metabolizing inorganic arsenic to DMA, and reported that DMA was the dominant arsenic species in the muscle tissue (Pizarro et al. 2004). Thus, DMA in chicken samples might result from metabolic conversion of inorganic arsenic present as a contaminant in roxarsone formulations, or metabolism of inorganic arsenic from other sources, such as drinking water and feed.

Comparison of raw and cooked samples

Total arsenic and inorganic arsenic concentrations were significantly higher and concentrations of roxarsone and the unknown arsenic species were significantly lower in cooked chicken meat samples compared with raw samples (Table 4, Figure 1A). Scatterplots displaying the impact of cooking on inorganic arsenic concentrations are presented by package label and by roxarsone detection in Figures 1B and 1C, respectively (scatterplots for total arsenic, roxarsone, DMA and the unknown species are presented in Supplemental Material, Figure S3). DMA concentrations were similar in raw and cooked samples. These results suggest that roxarsone and the unknown species may degrade into inorganic arsenic species during cooking. This hypothesis was investigated by comparing concentrations of roxarsone, unknown arsenic species, and inorganic arsenic in the same single freeze-dried raw chicken breast sample (in triplicate) before and after heating at 175 ºC for 30 minutes. In this experiment, concentrations of roxarsone and the

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unknown arsenic species decreased from 20 µg kg^{-1} (dry mass) and 10 µg kg^{-1}, respectively, in the raw chicken to <2 µg kg^{-1} in the "cooked" chicken, while inorganic arsenic increased from 11 to 42 µg kg^{-1}.

Risk analysis

Compared to consumers of organic chicken, we estimate that an 80 kg person (United States Environmental Protection Agency 2011a) consuming an average of 0.0824 kg chicken per day (United States Environmental Protection Agency 2011b) from conventional producers without policies prohibiting arsenical drug use (i.e., with a geometric mean inorganic arsenic concentration of 0.002 mg kg^{-1}) would ingest an additional 0.115 µg inorganic arsenic per day, resulting in a lifetime average daily dose of 3.71×10^{-5} mg kgBW^{-1} day^{-1}. Based on the EPA's proposed cancer slope factor for inorganic arsenic of 25.7 (mg kgBW^{-1}day^{-1})$^{-1}$ (United States Environmental Protection Agency 2010), average daily exposure at this level this would result in approximately 3.7 additional cases of bladder and/or lung cancer per 100,000 persons with lifetime exposure. When applied to the US population in 2011 (United States Census Bureau 2012), 75% of whom are estimated to be chicken consumers (United States Environmental Protection Agency 2011b), our estimates suggest that industry-wide use of arsenical drugs could result in 8,661 additional cases of cancer over 70 years, or an average of 124 cancers per year. This scenario represents the estimated increase in cancer cases if arsenical drugs are used in all domestically-produced poultry compared with cases expected with no use. The scenario does not account for consumers with high rates of chicken consumption, which have been estimated to be 3 and 6 times higher for those in the 95th and 99th percentiles of consumption compared with the typical consumer (Lasky et al. 2004). It is also important to note, however, that this analysis relies upon a proposed cancer slope factor derived based upon women, who appear to be more

sensitive than men with regard to bladder and lung cancers resulting from arsenic exposure (United States Environmental Protection Agency 2010). Given potential exposure differentials and sensitivity to arsenic exposure, some uncertainty exists in the magnitude of the cancer burden.

DISCUSSION

To our knowledge, this is the first study to characterize inorganic arsenic concentrations in grocery store chicken meat produced with and without arsenical drugs. In our study, samples with detectable roxarsone (presumably representing chicken treated with arsenical drugs) had higher inorganic arsenic concentrations than samples without detectable roxarsone. Roxarsone was detected in 20 of 40 conventional chicken meat samples, in one of 13 conventional antibiotic-free samples, and in none of the 25 organic samples tested. Conventional samples had higher inorganic arsenic concentrations than conventional antibiotic-free and organic samples. Our results also suggest that cooking chicken alters the arsenic species profile, increasing the inorganic fraction, potentially due to conversion of residual roxarsone and other uncharacterized arsenic species into arsenate and arsenite. Taken together, these findings suggest that the use of arsenic-based drugs in chicken production results in dietary exposures to inorganic arsenic.

While it is possible that non-pharmaceutical sources of arsenic, such as drinking water, may contribute to arsenic exposures during the production of chickens, and thus play some role in residual arsenic found in meat, we believe that such exposures are unlikely to be fully responsible for the differences we observed between different types of samples, as the rate of addition of roxarsone to animal feed is between 22.7 and 45.5 ppm (Food and Drug Administration 2012b).

Dietary and environmental contributors to population inorganic arsenic exposure include drinking water (Smith et al. 1992), rice (Meharg and Rahman 2003), and other foods (Xue et al. 2010). Inorganic arsenic in those sources tends to originate from naturally-occurring geologic arsenic deposits (Welch et al. 2000) or environmental contamination from heavy industry or historic pesticide use (Meharg and Hartley-Whitaker 2002). In contrast, arsenical poultry drugs are deliberately administered to animals intended for human consumption. Consequently, exposures resulting from use of these drugs are far more controllable than exposures from environmental sources. Few studies have looked specifically at the contribution of poultry to dietary arsenic intake, but an examination of individual food items as predictors of urinary arsenic in participants enrolled in a bladder cancer case-control study in Michigan found near significant associations between dietary intake of chicken and total arsenic ($p = 0.086$) and DMA ($p = 0.087$), but not arsenobetaine (Rivera-Núñez et al. 2011).

The FDA has not established safety standards for inorganic arsenic in foods, including rice, juice, chicken, or other foods potentially contaminated by arsenic. The FDA tolerances for total arsenic residues in poultry products (0.5 and 2 mg kg^{-1} for muscle and liver tissues, respectively) were established in the 1950s (Food and Drug Administration 2012a). In 2011, following a roxarsone feeding study, the FDA Center for Veterinary Medicine (CVM) indicated that "CVM has determined that a safe level of inorganic arsenic [in chicken meat] is << 1 ppb" (Food and Drug Administration 2011b). FDA later revised this statement, removing language suggesting a safe concentration and noting that "any new animal drug that contributes to the overall inorganic arsenic burden is of potential concern" (Food and Drug Administration 2011a). In our study, inorganic arsenic concentrations in 94% of organic, 88% of antibiotic-free, and 93% of samples from producers with policies against arsenical drug use were lower than 1 µg kg^{1}. Conversely,

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70% of samples of chicken meat from conventional producers without prohibitory arsenical drug policies exceeded this threshold.

Our study provides strong evidence that arsenic-based drugs used in poultry production result in increased inorganic arsenic concentrations in chicken meat. Previous research by the FDA has shown that inorganic arsenic concentrations were increased in the livers of chickens fed roxarsone (Food and Drug Administration 2011b), and *Clostridia* species of bacteria present in the poultry cecum and in poultry waste have been shown to be capable of transforming roxarsone into inorganic arsenic (Stolz et al. 2007). In July 2011, as a result of the FDA findings of inorganic arsenic in chicken livers, the leading US marketer of roxarsone suspended its sale from the domestic market, pending further study (Harris and Grady 2011). However, international sales of roxarsone, which is believed to be widely used in poultry production in countries around the world, have continued (Harris and Grady 2011). Moreover, nitarsone, another FDA-approved arsenic-based poultry drug that is similar to roxarsone, continues to be available for use in conventional poultry production in the US (Pfizer Animal Health 2012).

The present study employed highly sensitive laboratory techniques to characterize inorganic arsenic, roxarsone, and other arsenic species in chicken meat. To our knowledge, it is the first study to quantify roxarsone residues in chicken meat; given that roxarsone is a non-naturally occurring compound, its detection in chicken meat is consistent with its deliberate use as a feed additive. By analyzing cooked chicken meat, we also provide data on total arsenic concentrations and species that are directly relevant for human consumption. Moreover, we tested 63 paired raw and cooked samples to evaluate potential cooking-induced changes in the arsenic species profile.

Due to budgetary constraints, we speciated arsenic only in samples with total arsenic concentrations above 10 µg kg^{-1} (dry weight); thus, uncertainty remains with regard to the species profile below this threshold. Despite this limitation, we had sufficient power to detect statistically significant differences in arsenic species across sample classifications. In this study, we only measured arsenic in chicken breast meat. Additional measurements are needed to estimate arsenic concentrations in other chicken tissues such as skin, wings, thighs, and legs. There is also some uncertainty associated with the selected cancer slope factor, which has yet to be finalized. This selection, however, does reflect EPA's latest interpretation of the epidemiologic evidence and corresponds to internal, rather than skin, cancers.

Conclusions

Our study provides strong evidence that the use of arsenic-based drugs contributes to dietary inorganic arsenic exposure in consumers of conventionally-produced chickens. Our findings suggest that eliminating the use of arsenic-based drugs in food animal production could reduce the burden of arsenic-related disease in the US population.

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Table 1. Previous studies of arsenic in poultry

Study	Analytical method	Tissue	N	As$_t$ (μg kg^{-1})	As$_i$ (μg kg^{-1})
Morrison et al. (1969)[a]	NR[b]	Liver	181	150 - 790	N/A
		Kidney	117	< 100 - 240	N/A
		Muscle	181	< 100	N/A
		Skin	144	< 100	N/A
Lasky et al. (2004)	NR	Liver	20,559	330 - 430[c]	N/A
		Muscle (estimated)	20,559	NR	N/A
Wallinga (2006)	ICP-MS	Muscle (uncooked)	151	ND - 21.2	N/A
		Muscle (cooked)	90	ND - 46.5	N/A
Food and Drug Administration (2011)[d]	ICP-MS and IC-ICP-MS	Liver	21	275 - 2940	0.1 - 9.1
		Muscle (uncooked)	21	13.9 - 48.4	N/A

[a] All chickens in Morrison (1969) were treated with roxarsone, and FDA (2011) was an experimental study using roxarsone-treated and control chickens. The Lasky et al. (2004) and Wallinga (2006) studies were not able to definitively determine which chicken samples had been treated with roxarsone.

[b] NR = not reported, ICP-MS = inductively coupled plasma mass spectrometry, IC-ICP-MS = ion chromatography inductively coupled plasma mass spectrometry

[c] Annual mean concentrations from National Residue Program monitoring. Full range not reported.

[d] Results presented are for roxarsone-treated chickens with a 5-day withdrawal period.

Table 2. Geometric mean (95% CI) of arsenic concentrations (in µg kg^{-1}) in cooked chicken meat by sample characteristics[a]

Chicken sample classification	Total arsenic					Speciated arsenic			
	N	Total As	N	iAs	DMA	N (%) Roxarsone (+)	Roxarsone	N (%) Unknown species (+)	Unknown species
All	140	3.0 (2.5, 3.6)	78	1.1 (0.9, 1.3)	3.5 (3.1, 4.0)	19 (24.3)	0.6 (0.5, 0.7)	13 (16.7)	0.3 (0.2, 0.3)
Package label									
Conventional	69	3.4 (2.5, 4.5)	40	1.8 (1.4, 2.3)	2.6 (2.1, 3.1)	18 (45.0)	0.7 (0.6, 0.9)	13 (32.5)	0.3 (0.2, 0.3)
Conventional antibiotic-free	34	2.0 (1.2, 3.0)	13	0.7 (0.5, 1.0)	4.2 (3.1, 5.6)	1 (7.7)	0.5 (0.4, 0.6)	0 (0.0)	--
Organic	37	3.4 (2.6, 4.5)	25	0.6 (0.5, 0.8)	4.9 (4.1, 5.9)	0 (0.0)	--[b]	0 (0.0)	--
Producer arsenical policy[c]									
No known policy	46	5.6 (4.3, 7.4)	34	2.0 (1.6, 2.5)	3.8 (3.0, 4.9)	18 (52.9)	0.7 (0.6, 1.0)	13 (38.2)	0.4 (0.3, 0.5)
Conventional with prohibiting policy	57	1.6 (1.2, 2.3)	19	0.7 (0.5, 0.9)	2.6 (2.1, 3.2)	1 (6.3)	0.5 (0.4, 0.6)	0 (0.0)	--
Roxarsone detection									
Negative	121	2.4 (2.0, 2.9)	59	0.8 (0.7, 1.0)	3.6 (3.1, 4.2)	0 (0.0)	--	0 (0.0)	--
Positive	19	10.2 (7.8, 13.4)	19	2.3 (1.7, 3.1)	3.2 (2.5, 4.0)	19 (100.0)	1.3 (1.0, 1.7)	13 (68.4)	0.7 (0.4, 1.0)
Metropolitan area									
Atlanta, GA	13	2.2 (1.0, 5.0)	9	0.7 (0.4, 1.3)	3.2 (2.4, 4.3)	2 (25.0)	0.6 (0.3, 1.0)	2 (25.0)	0.3 (0.2, 0.8)
Austin, TX	17	3.3 (2.0, 5.6)	9	1.0 (0.5, 1.9)	2.9 (2.0, 4.4)	5 (55.6)	0.6 (0.4, 1.2)	4 (44.4)	0.4 (0.2, 0.7)
Baltimore, MD	13	4.1 (2.1, 7.9)	9	1.9 (1.2, 3.0)	3.0 (1.5, 6.0)	3 (33.3)	0.6 (0.4, 1.0)	2 (22.2)	0.3 (0.2, 0.5)
Denver, CO	17	3.9 (2.2, 6.8)	11	1.4 (0.8, 2.6)	3.5 (2.5, 4.8)	3 (27.3)	0.6 (0.5, 0.8)	0 (0.0)	--
Fayetteville, AK	14	3.1 (1.8, 5.5)	9	0.9 (0.4, 2.1)	2.3 (1.5, 3.7)	1 (12.5)	0.5 (0.4, 0.6)	0 (0.0)	--
Flagstaff, AZ	12	5.8 (3.6, 9.5)	9	1.4 (0.8, 1.8)	4.7 (3.2, 6.7)	3 33.3	0.7 (0.4, 1.3)	3 (33.3)	0.4 (0.2, 0.8)
Los Angeles, CA	12	3.9 (2.2, 7.0)	7	1.3 (0.6, 2.8)	4.4 (2.8, 6.8)	2 (28.6)	0.7 (0.3, 1.4)	2 (47.1)	0.4 (0.2, 0.9)
New York, NY	16	1.0 (0.4, 2.4)	5	0.8 (0.5, 1.4)	7.7 (4.1, 14.5)	0 (0.0)	--	0 (0.0)	--
San Francisco, CA	13	2.7 (1.9, 3.8)	6	0.8 (0.5, 1.2)	3.4 (2.7, 4.3)	0 (0.0)	--	0 (0.0)	--
Seattle, WA	13	2.6 (2.0, 3.4)	4	0.6 (0.5, 0.8)	3.2 (2.1, 6.7)	0 (0.0)	--	0 (0.0)	--

[a] Limits of detection (LOD) were 1 µg/kg DW for total arsenic, inorganic arsenic, and DMA and 2 µg/kg DW for roxarsone. Samples below the LOD were imputed as the corresponding detection limit divided by the square root of two.

[b] The geometric means for roxarsone and the unknown species were not calculated when all samples were below the limit of detection.

[c] Organic samples are not re-listed here, as arsenical drugs are not permitted for use in USDA Organic-certified chicken.

Table 3. Correlation matrices for arsenic species in raw and cooked chicken meat samples

	Total As	iAs	DMA$_V$	Roxarsone[a]	Unknown[a]
Raw Samples (n=65)					
Total As	1.00	-	-	-	-
iAs	0.62	1.00	-	-	-
DMA	0.71	0.36	1.00	-	-
Roxarsone	0.61	0.75	0.17	1.00	-
Unknown	0.55	0.63	0.11	0.83	1.00
Cooked Samples (n=78)					
Total As	1.00	-	-	-	-
iAs	0.75	1.00	-	-	-
DMA	0.65	0.33	1.00	-	-
Roxarsone	0.65	0.68	0.25	1.00	-
Unknown	0.56	0.52	0.23	0.82	1.00

[a] For roxarsone and unknown species, correlation analyses were restricted to samples with a positive detection (N = 30 for roxarsone and N = 24 for unknown species).
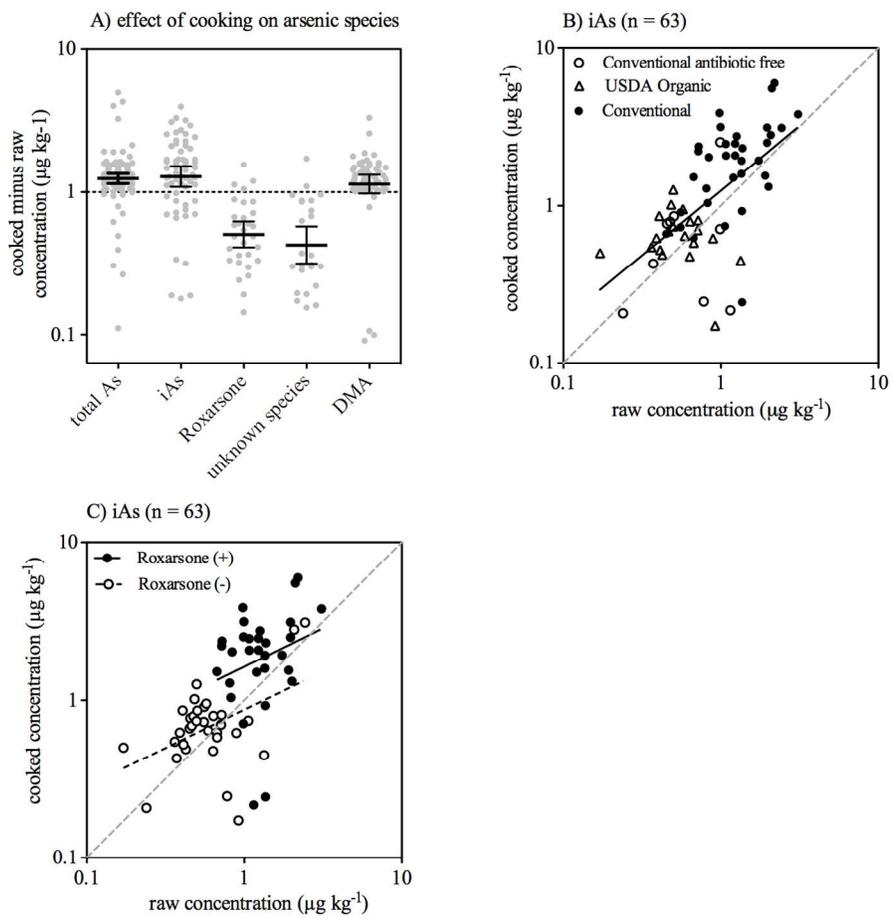
Table 4. Paired t-test comparisons of arsenic species concentrations (in µg kg-1) in paired raw and cooked chicken meat samples

As species	N pairs	Raw Geometric Mean (95% CI)	Cooked Geometric Mean (95% CI)	p-value	% change
Total As	102	3.0 (2.5 - 3.6)	3.8 (3.2 - 4.5)	< 0.001	(+) 21.1%
iAs	63	0.8 (0.7 - 1.0)	1.1 (0.9 - 1.3)	0.004	(+) 27.2%
DMA$_V$	63	2.7 (2.4 - 3.1)	3.1 (2.5 -3.8)	0.09	(+) 12.9%
Roxarsone[a]	30	1.8 (1.4 - 2.2)	1.0 (0.7 - 1.3)	< 0.001	(-) 44.1%
Unknown[a]	24	1.3 (1.0 - 1.5)	0.8 (0.5 - 1.1)	<0.001	(-) 38.4%

[a]Analyses for roxarsone and unknown species were restricted to pairs of samples with at least one positive detection

FIGURE LEGEND

Figure 1. Means and 95% confidence intervals for arsenic species are reported for the difference between pairs of cooked and raw samples (A). Scatterplots of cooked vs. raw concentrations of inorganic arsenic by package label: closed circles represent conventional chicken, open circles for conventional antibiotic free chicken, and open triangles for organic chicken (B). Scatterplots of cooked vs. raw concentrations of inorganic arsenic by roxarsone presence (closed circles) or absence (open circles) (C).

A) effect of cooking on arsenic species

B) iAs (n = 63)

C) iAs (n = 63)

138x137mm (300 x 300 DPI)