Arsenic in Rice and Rice Products
Risk Assessment Report

Center for Food Safety and Applied Nutrition
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ABBREVIATIONS AND ACRONYMS

Abbreviation/Acronym	Definition
AIK	Akaike's Information Criterion
AQP9	Aquaporin 9
As	Arsenic
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
$BMDL_1$	Benchmark Dose Lower Confidence Limit for a 1% Change in Response Rate
BMDS	Benchmark Dose Software
CCA	Chromated Copper Arsenate
CDC	Centers for Disease Control and Prevention
CFSAN	Center for Food Safety and Applied Nutrition
CI	Confidence Interval
CNNHS	China National Nutrition and Health Survey
CSFII	Continuing Survey of Food Intake by Individuals
DMA	Dimethylated Arsenic
DMA^{III} or DMA (III)	Dimethylarsonous Acid
DMA^{V} or DMA (V)	Dimethylarsinic Acid
DNA	Deoxyribonucleic Acid
ED01	Effective Dose for 1%
EFSA	European Food Safety Authority
ENCAT	Catalan Nutrition Survey
ENPP2	Ectonucleotide Pyrophospate/Phosphodiesterase 2 also called Autotaxin
EO	Eating Occasion
EPA	Environmental Protection Agency
ERS	Economic Research Service
FAO	Food and Agriculture Organization
FARE	Food Analysis and Residue Evaluation
FCID	Food Commodity Intake Database
FDA	Food and Drug Administration
GI	Gastrointestinal
HEALS	Health Effects of Arsenic Longitudinal Study
HPLC-ICP-MS	High Performance Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometry
IARC	International Agency for Research on Cancer
iAs	Inorganic Arsenic
IC-ICP-DRC-MS	Ion Chromatography-Inductively Coupled Plasma-Dynamic Reaction Cell-Mass Spectrometry
ICP-DRC-MS	Inductively Coupled Plasma-Dynamic Reaction Cell-Mass Spectrometry
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IRIS	EPA's Integrated Risk Information System

Abbreviation/Acronym	Definition
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LED01	Lower Bound of the Effective Dose for 1% (ED01)
LOD	Limit of Detection
MCL	Maximum Contaminant Level
MLE	Maximum Likelihood Estimator
MMA	Monomethylated Arsenic
MMA^{III} or MMA (III)	Monomethylarsonous Acid
MMA^{V} or MMA (V)	Monomethylarsonic Acid
MOA	Mode of Action
MRL	Minimal Risk Level
MSMA	Monosodium Methanearsonate
N/A	Not Applicable
NAS	National Academy of Sciences
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Science
NRC	National Research Council
NOAEL	No Observed Adverse Effect Level
OMB	Office of Management and Budget
OPP	Office of Pesticide Programs
OR	Odds Ratio
ORNL	Oak Ridge National Laboratories
PAF	Population Attributable Fractions
PAH	Polycyclic Aromatic Hydrocarbon
PCB	Polychlorinated Biphenyl
ppb	Parts Per Billion
ppm	Parts Per Million
RfD	Reference Dose
RR	Relative Risk
SEM	Standard Error of the Mean
T	Tablespoon
TDI	Tolerable Daily Intake
TDS	Total Diet Study
TMAO	Trimethylarsine Oxide
USDA	United States Department of Agriculture
WHO	World Health Organization
WWEIA	What We Eat In America

EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) is issuing for public comment this assessment of health risks from inorganic arsenic in rice and products that contain rice (referred to in the report as "rice products"). The risk assessment was conducted by FDA's Center for Food Safety and Applied Nutrition, in consultation with the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the FDA National Center for Toxicological Research, and the Environmental Protection Agency.

The risk assessment provides: (1) a quantitative (that is, mathematical) estimate of cancer occurrence from long-term exposure to inorganic arsenic in rice and rice products; and (2) a qualitative assessment – a review and evaluation of the scientific literature – of certain non-cancer risks, in certain susceptible life stages, from inorganic arsenic in rice and rice products. The mathematical model we developed for the quantitative risk assessment not only estimates risk from various kinds of rice and rice products, but also predicts changes in risk resulting from various mitigation actions, based on the best available science.

The results of the risk assessment are the predicted lifetime risk, expressed as number of lung and bladder cancer cases per million people, given in two ways: (1) the average person's estimated risk attributable to long-term exposure to rice and rice products, over a lifetime – the "per capita" risk – and (2) the estimated lifetime risk posed by eating a given amount of rice or rice product every day, on average– the "per eating occasion" risk. The former reflects a population's risk; the latter reflects an individual's risk.

We chose to focus on inorganic arsenic, because it is the primary toxic type of arsenic, in contrast to organic arsenic. We focused on rice and rice products, because evidence from FDA's Total Diet Study – an ongoing survey and analysis of the average American diet – revealed that arsenic levels, although varying, tend to be higher in these foods than in others, and rice products are common in the average American diet.

The quantitative risk assessment examines lung cancer and bladder cancer, which provide the best evidence of low-dose cancer effects. The qualitative risk assessment describes our literature review and evaluation of potential non-cancer health risks from arsenic in rice and rice products in two vulnerable populations: (1) those exposed to arsenic while in the womb, through maternal intake of arsenic-containing rice and (2) early childhood, including infancy.

Summary of Cancer Estimates and Predictions

There are two forms of arsenic in food, inorganic and organic. Inorganic arsenic levels reported in these products is not a concern in terms of immediate toxicity at the levels seen in food, but may be a health concern when they are consumed long-term. Organic arsenic – monomethylated and dimethylated arsenic, or MMA and DMA, are also found in rice and rice products. Current research suggests that MMA and DMA, when ingested directly from food, undergo limited metabolism.

Calculating the kinds of estimates and predictions below involves varying amounts of uncertainty, because, for example, some data we need may not yet be available in the scientific literature. We must substitute educated assumptions and professional judgment in these instances, based on the best available evidence. Although the risk assessment characterizes the uncertainty associated with the risk estimates and predictions, we present only the estimates and predictions themselves in this executive summary (see Chapter 5 Risk Characterization of Lung and Bladder Cancer, for additional details including the confidence limits).

We knew that arsenic was present in a variety of foods in the U.S. diet but until recently there were not enough data to determine the amount that is inorganic versus organic. To provide information for our estimates of dietary intake of arsenic from rice and rice products, we measured the arsenic levels in these foods. We found that average concentrations of inorganic arsenic – the more toxic form of arsenic – were as follows:

- 92 parts per billion (ppb) in white rice
- 154 ppb in brown rice
- 104 ppb in infants' dry white-rice cereal
- 119 ppb in infants' dry brown-rice cereal

The model we developed for the quantitative risk assessment adjusted for the bioavailability of arsenic – the amount of its absorption by the body after it is ingested. Our review of the literature indicates that inorganic arsenic is bioavailable.

- Although the average concentration is higher in brown rice than in white rice, the majority of the risk is from white rice, because more white rice is eaten (see Tables 4.3 and 4.6).

- The lung cancer and bladder cancer risk (hereafter shortened to "cancer risk") attributable to lifetime exposure to all rice and rice products is a small portion of all cases of these cancers, at 39 cases per million people (10 cases/million bladder cancer and 29 cases/million lung cancer) (see Table 5.3). To put this in perspective, the total numbers of lung and bladder cancer cases, from all causes, are 90,000 per million people over a lifetime .

- The model suggests that the risk increases almost proportionally with increases in daily servings (see Table 5.9). The average American diet (per capita) includes less than one serving of rice and rice products per day. If the amount was increased to an average of one serving per day, the lifetime cancer risk from arsenic in rice and rice products would increase to between 74 and 184 cases per million people, depending on the type of rice consumed (see Table 5.2). .

- Data indicate that rinsing/cooking practices have variable impact on reducing arsenic levels in rice. However, these practices also reduce enriched iron, folate, thiamin and niacin.

- The predicted risk of developing cancer at some point in life after having been exposed to inorganic arsenic in rice only during infancy increases with the frequency of weekly servings (see Table 5.9), as shown below.

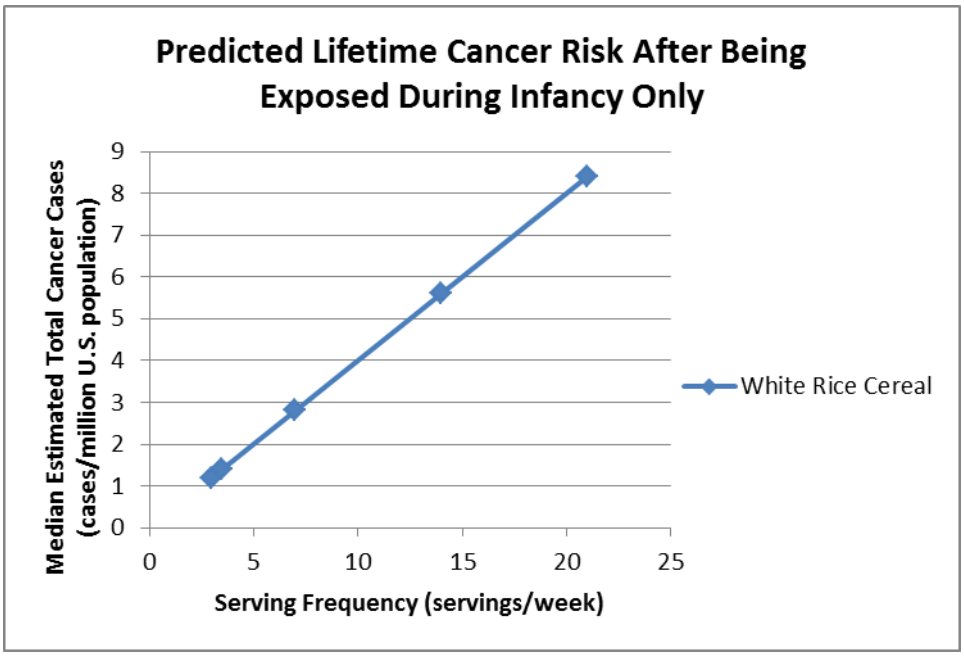

Figure 1 Predicted Lifetime Lung and Bladder Cancer Risk After Exposure to Inorganic Arsenic During Infancy

- The predicted risk of developing cancer at some point in life after having been exposed to inorganic arsenic in rice from ages 0 to 6 increases with the frequency of weekly servings (see Table 5.9), as shown in the following chart.

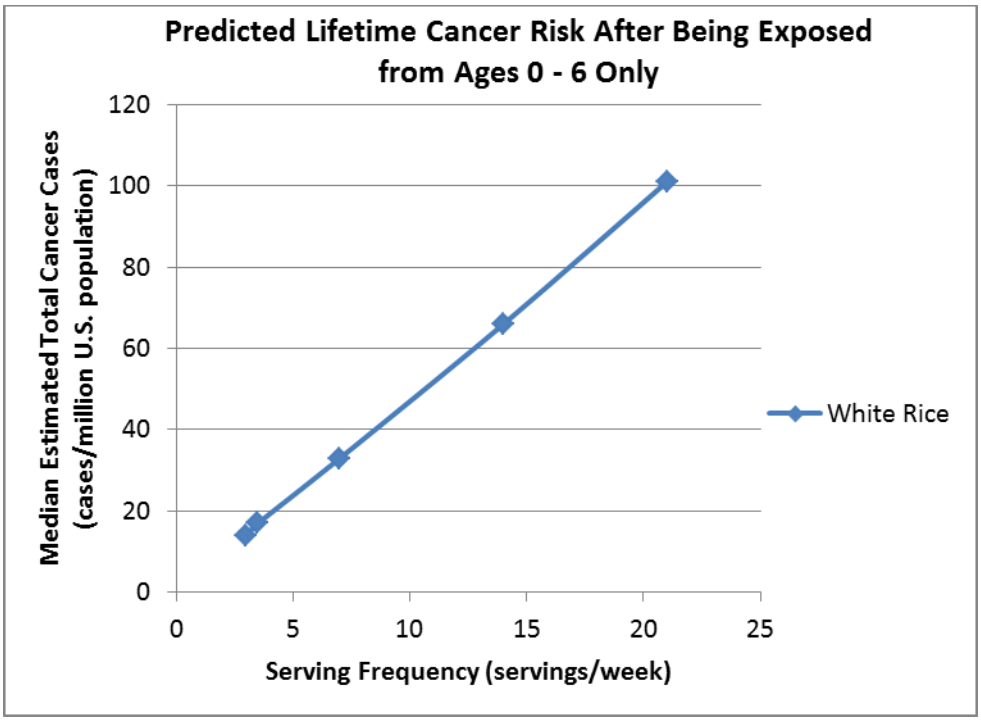

Figure 2. Predicted Lifetime Lung and Bladder Cancer Risk After Exposure to Inorganic Arsenic During Ages 0 – 6

Reducing inorganic arsenic exposure by either reducing consumption of rice and rice products or limiting the level of inorganic arsenic in rice grain and rice products would decrease lifetime cancer risk, as follows:

- In the general population, limiting levels of inorganic arsenic to 200 ppb or higher would not change the cancer risk significantly. Setting a limit below 200 ppb of inorganic arsenic in rice and rice products would decrease the risk. Setting a limit of 150 ppb of inorganic arsenic in rice and rice products would decrease the risk between 0% and 23%. The risk reduction is between 2% and 47% at a limit of 100 ppb of inorganic arsenic in rice and rice products. Finally setting a limit at 75 ppb of inorganic arsenic in rice and rice products would decrease the risk between 17% and 79%. The percentage of risk reduction is dependent on the product (see Table 5.6).

- Setting a maximum level for inorganic arsenic in rice and rice products could affect availability in the U.S. market. For example, were we to set a maximum level of 100 ppb in these foods, the availability in the marketplace might decrease by 4% to 93%, depending on the type of rice.

- In the general population, the cancer risk would decrease in proportion to decreases in serving size and frequency of consumption of rice and rice products. Conversely, the risk

would double over a lifetime if the consumption frequency were increased from 1 serving per day to 2 servings per day during that entire period (see Table 5.9).

- Eliminating rice and rice products from the diets of infants and of children up to 6 years old could reduce the lifetime cancer risk from inorganic arsenic in rice and rice products by 6% and 23%, respectively. In other words, the risk model predicts that an infant not fed any rice or rice products has an approximately 6% lower chance of developing lung or bladder cancer from arsenic contamination of these foods, over the lifetime, compared with an infant who is fed these products (see Table 5.7).

Summary of Qualitative Assessment of Non-cancer Risk

Approximately 90% of pregnant women eat rice grain or rice products. Considering rice grain, each serving increases a woman's daily exposure to inorganic arsenic by approximately 5.2 – 7.8 µg/serving (see Table 6.4). Our literature review indicates that fetuses may have increased susceptibility to adverse health effects from maternal inorganic arsenic intake.

The literature also suggests that exposure to inorganic arsenic during infancy and early childhood can have neurotoxic effects, although whether these effects are lasting is unclear. At this time, a quantitative assessment of non-cancer health effects associated with arsenic exposure in utero (through maternal intake) and during infancy and early childhood has not yet been conducted. We are working with EPA on this issue as data become available.

Research Needs

In conducting the risk assessment, we identified areas in need of research, to provide data not currently available in the scientific literature. Additional data on the following topics would advance our ability to estimate risks from dietary arsenic and predict the most effective mitigations, to provide risk managers with science-based options for reducing the risk:

- new surveys on representative data samples, including speciation of arsenic in commonly consumed foods;

- meta-analyses of epidemiological studies, to help determine the amount of dietary arsenic linked to health effects, including those not assessed in the current risk assessment, such as cardiovascular effects and diabetes;

- early-life exposure to arsenic, using models that include timing and amount of exposure as variables;

- adverse health effects of inorganic arsenic in certain susceptible life stages;
- improved methods for characterization of exposure from epidemiological data on dose-response; and
- agricultural and processing practices that would reduce arsenic content of rice.

Next Steps

This risk assessment builds on previous research and collaborations by FDA and other agencies. As an important part of the process, and in the interest of transparency, the report will now undergo public comment and the risk assessment and report may be revised accordingly.

In addition, FDA will continue to monitor important research in this area, including ongoing work by the National Academies of Sciences (NAS) Board on Environmental Studies and Toxicology, which is currently reviewing EPA's work on inorganic arsenic, specifically on EPA's IRIS Toxicological Assessments of Inorganic Arsenic.

1 INTRODUCTION

The U.S. Food and Drug Administration's Center for Food Safety and Applied Nutrition (FDA-CFSAN; i.e., "we") conducted this risk assessment in consultation with other federal agencies, including the National Institute of Environmental Health Sciences (NIEHS) and the National Center for Environmental Assessment (NCEA), Office of Research and Development (ORD), at the U.S. Environmental Protection Agency (EPA). The purpose of this assessment is to examine available scientific data and information, to provide quantitative estimates of cancer risk presented by long-term exposure to inorganic arsenic in rice grain and products that include rice as an ingredient (hereafter referred to as rice products). In addition, the risk assessment qualitatively addresses certain possible non-cancer health effects attributable to exposure to inorganic arsenic in rice grain and rice products during pregnancy, infancy, and/or early childhood (from birth to 6 years of age). This examination of the current science and predictive model are among the tools we will use to evaluate current and potential policies, programs, and mandatory or voluntary practices for minimizing the public-health impact of this food contaminant. This work is a comprehensive risk assessment that builds upon previously published assessments and evaluations, and incorporates new information (EPA, 2007; EFSA, 2009; JECFA, 2011; IARC, 2012; Carrington *et al.*, 2013; NRC, 2013).

On September 6, 2013, FDA issued the results of a survey of approximately 1,300 samples of rice and rice products (available at http://www.fda.gov/food/foodborneillnesscontaminants/metals/ucm319870.htm). The survey indicated that inorganic arsenic varies (from <1 to 545 parts per billion, hereafter abbreviated "ppb," of inorganic arsenic) among and within the different categories of rice grain and rice products. When we issued the results of the survey, we also announced plans to conduct a risk assessment that considered long-term exposure to arsenic from consumption of rice grain and rice products. We conducted that risk assessment and are hereby issuing this report for public comment. On considering public comments, external peer review comments, and any newly available information, we will issue a final report.

Plants vary considerably in their ability to take up and accumulate arsenic. Compared with other cereals, such as wheat and barley, rice has much higher levels of arsenic. The elevated arsenic is due to rice being the only major cereal crop grown under flooded conditions, leading to high arsenic availability and high concentrations close to the root (Zhao *et al.*, 2010).

Inorganic arsenic is associated with many adverse health effects. These health endpoints and the level of evidence linking each effect to inorganic arsenic exposure are extensively discussed in the National Research Council (NRC) Interim Report on Inorganic Arsenic (2013). Evidence linking many of these endpoints to inorganic arsenic is emerging in the scientific literature; for

example, cardiovascular disease, diabetes, and immunologic effects. We determined that it would not be in the best interest of public health to wait to include all endpoints in this risk assessment, because it would add considerable time to the completion of our assessment. Instead, we focused on well-documented cancer effects for the general population and sensitive non-cancer health effects regarding three susceptible life stages: pregnancy, infancy, and early childhood. We continue to follow the literature regarding the effects of exposure to inorganic arsenic and of other non-cancer health effects and to work with other agencies on the risk to consumers.

We also concluded that it would be time-and resource-intensive to monitor every food commodity reported to contain inorganic arsenic. We therefore chose to focus on rice and rice products for this risk assessment, because, in FDA's Total Diet Study (TDS) sampling, rice had the highest levels of total arsenic, except seafood, compared with other food commodities, and rice is an ingredient of many products that consumers routinely eat.

We plan to continue to monitor the scientific literature for additional research on adverse health endpoints associated with inorganic arsenic and on levels of inorganic arsenic in other food commodities, through the TDS and directed surveillance programs. Additionally, we plan to continue to work with our federal partners, including EPA, NIEHS, CDC, and USDA, as new data emerge on the adverse health endpoints associated with inorganic arsenic and on mitigation strategies for lowering levels of inorganic arsenic in food.

1.1 PROCESS FOR CONDUCTING RISK ASSESSMENTS

We have adopted the risk analysis approach recommended by Codex Alimentarius (Codex, 2007) for addressing complex food-safety problems. The Codex Alimentarius Commission is an intergovernmental body, with more than 170 member countries, within the framework of the Joint Food Standards Programme established by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), whose collective purpose is to protect the health of consumers and ensure fair practices in the food trade. The Commission also promotes coordination of all food-standards work undertaken by international governmental and non-governmental organizations. The Codex Alimentarius is a result of the Commission's work: a collection of internationally adopted food standards, guidelines, codes of practice, and other recommendations.

The risk analysis approach is an integrated process of risk assessment, risk management, and risk communication that facilitates the translation of scientific knowledge into policy. Within the risk analysis process, risk assessment improves understanding of disease occurrence, relative to the complex interactions of the hazard, human host, and food that are involved in a given food-safety

issue. As a structured and systematic process, risk assessment provides the means to link events in the food-supply system (such as contamination, concentration of hazards in foods) to public-health metrics (such as illness, death). Additionally, quantitative risk assessment models provide a means of predicting the effectiveness of interventions, mitigations, or control measures for preventing and reducing disease.

FDA will consider the risk assessment, along with other relevant information, in the development of risk-management options and the final selection of an option or combination of options to be implemented. An important part of this process is to periodically evaluate the effectiveness of the risk-management decisions that were made to achieve the stated public-health goal.

Risk communication includes the need to identify and understand stakeholder concerns and information needs and perceptions and to develop public-health messages based on the results of the risk assessment and on risk-management plans. Active communication in this regard allows for a high level of transparency and encourages stakeholder participation, and promotes credibility and scientific accountability regarding our work and our decisions.

The process we use for conducting and managing risk assessment includes five phases:

Phase 1: Preliminary activities

Phase 2: Data collection, analysis, and evaluation

Phase 3: Model development and report preparation

Phase 4: Review (internal and external)

Phase 5: Issuance of report

Details about the FDA-CFSAN process, described in the FDA (2002) framework document, are available at http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/ucm242929.htm.

1.2 OBJECTIVES AND SCOPE OF THE RISK ASSESSMENT

As noted in the FDA (2002) framework document, among the duties of risk managers, during the initiation and preliminary activities of a risk assessment, is to formulate the questions to be addressed and key assumptions. The initial questions posed by the risk managers for this risk assessment included the following:

1) Which foods or food products contribute the most to arsenic exposure from the diet?

2) What are the adverse health effects from exposure to different forms of arsenic (inorganic vs. organic) in rice?

3) Are pregnancy, infancy, and/or early childhood periods of greater susceptibility to non-cancer effects of oral exposure to inorganic arsenic, and if so, can the risks be quantified?

Additional questions, specific to the risk of cancer from exposure to inorganic arsenic in rice grain and rice products, included the following:

4) What are the predicted risks of cancer from long-term exposure to inorganic arsenic from consuming rice grain and rice products, for the total U.S. population, and the risk attributable to exposure only during infancy and childhood?

5) What is the predicted lifetime risk of cancer from exposure to inorganic arsenic from rice grain and rice products, expressed on the basis of the population (i.e., cases per million) and the individual (i.e., cases per serving)?

6) Are there differences in the predicted risk from consumption of different types of rice grain (e.g., white rice, brown rice)?

7) What is the impact, on the predicted risk of cancer, from mitigations or interventions that reduce dietary exposure to inorganic arsenic from rice grain and rice products?

The objectives of this risk assessment are to assess the risk of adverse health effects associated with exposure to arsenic from consumption of rice grain and rice products and to examine how that risk may be mitigated. This risk assessment provides a scientific basis for the development of risk-management policy and consumer options for reducing exposure to arsenic from consumption of rice grain and rice products.

The two major components of the risk assessment are:

1) quantitative estimates of cancer occurrence from long-term exposure to inorganic arsenic in rice grain and rice products, and
2) a qualitative assessment of the risk of non-cancer health effects to certain susceptible life stages.

The scope of the quantitative risk assessment of cancer endpoints includes the following:

- Hazard: The focus is on inorganic arsenic.

- Food products: The focus is rice grain (including different types, such as white, brown, parboiled) and products that contain rice grain as an ingredient (e.g., cereals).

- Populations of interest: Total U.S. population, infants, children, and average- and higher-consumers of rice.

- Health effects of concern: Lung cancer, bladder cancer.

- Analysis outputs (results): Predicted lifetime risk of cancer cases per million and cancer cases associated with a single serving per day.

The scope of the qualitative risk assessment of non-cancer adverse health effects, in certain populations, includes the following:

- Hazard: The focus is on inorganic arsenic.

- Food products: The focus is rice grain (including different types, such as white, brown, parboiled) and products that contain rice grain as an ingredient, with emphasis on infant rice cereal.

- Life stages of interest: Pregnant women (i.e., effects on fetus), infants, and children.

- Health effects of concern: Adverse pregnancy outcomes and neurological effects in children.

- Analysis outputs (results): Qualitative assessment of the strength of evidence for adverse health effects associated with a single serving per day of either rice grain or rice products. See Appendix 9.14

The data used in this risk assessment were identified through comprehensive searches of the published literature and publicly available government reports. Inclusion criteria were used to select the data considered. Descriptions of the search methods and selection criteria are provided in the text and appendices, as noted in each section of the report.

1.3 COLLABORATIONS

Characterizing the risk to consumers from oral exposure to inorganic arsenic is complicated and involves the cooperation of many federal agencies. FDA monitors the published scientific literature for publications related to arsenic toxicity. FDA also monitors the food supply for levels of inorganic arsenic in different food commodities through its TDS, its Toxic Elements Programs (TEP), and direct surveillance activities. FDA has partnered with other federal agencies to coordinate this research and to collaborate on findings and recommendations. For example, FDA has been working closely with the EPA Integrated Risk Information System (IRIS) Program as EPA reassesses the cancer and non-cancer effects of exposure to inorganic arsenic, and FDA has followed closely the epidemiology research funded by NIEHS on arsenic effects on susceptible life stages. An evolving area is the methodology used to characterize the dose-response relationships for the toxic effects of arsenic. FDA is reviewing the recommendations from the NRC report entitled "Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic" and anticipates assisting EPA, where possible, in addressing research needs in response to that report (NRC, 2013). Similarly, EPA is closely following FDA's activities regarding the assessment of arsenic in food commodities.

As mandated by Congress, the National Academies of Sciences (NAS) Board on Environmental Studies and Toxicology is currently reviewing EPA's work on inorganic arsenic, specifically on EPA's IRIS Toxicological Assessments of Inorganic Arsenic. This study was initiated in July 2012.

The NAS committee on inorganic arsenic will provide recommendations on how critical scientific issues in assessing cancer and noncancer effects from oral exposure can be addressed in EPA's IRIS assessment. In November 2013, the NAS committee provided an interim report, "Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic," which FDA has used to inform our risk assessment. Following completion of the IRIS assessment, the NAS committee will review it to determine whether EPA adequately evaluated the scientific literature, used appropriate methodologies for deriving cancer and non-cancer reference values, and appropriately estimated and characterized dose-response relationships for cancer and non-cancer endpoints. FDA is working closely with EPA, and further research by FDA on this issue will benefit from these ongoing efforts among NAS, EPA, and FDA.

This risk assessment is based on the best science available at the time on risk of inorganic arsenic in rice and rice products. As with all FDA risk assessments, we are issuing this for public comment and will review new, significant scientific findings as they become available. In developing this risk assessment, we also considered comments that were submitted regarding the FDA risk assessment on arsenic in apple juice, released in July 2013 (Carrington *et al.*, 2013).

2 HAZARD IDENTIFICATION

This section provides current scientific information on the toxicities of arsenic, including inorganic arsenic (iAs), monomethylated arsenic (MMA) and dimethylated arsenic (DMA). The health effects of critical cancer and certain non-cancer endpoints associated with inorganic arsenic exposure are reviewed.

2.1 THE CONTAMINANT: ARSENIC

The summary in this section highlights key information about arsenic metabolism and toxicity and is not meant to be an extensive literature review

2.1.1 INTRODUCTION

Arsenic (As) is a naturally occurring element that is present in air, soil, water, and food. Arsenic exists in many chemical forms and valence states (-3, 0, +3 and +5). The forms fall broadly into two categories with public health relevance: inorganic and organic. Inorganic forms are considered a primary toxic form of arsenic; the common organic arsenic species (predominantly DMA) found in terrestrial ecosystems can also be toxic.

Human activities, such as burning of coal, oil, gasoline, and wood; mining; and the use of arsenic compounds as medicinals, herbicides, and wood preservatives [primarily chromated copper arsenate (CCA)] have contributed to the arsenic environmental burden. In the U.S., arsenic compounds are for use only by certified pesticide applicators and are no longer allowed for residential use as wood preservatives, although many CCA-treated wood products are still present in the environment. The organic arsenical monosodium methanearsonate (MSMA) is currently registered as a pesticide for use on cotton, golf courses, sod farms, and highway rights-of-way (EPA, 2013a).

Background concentrations of arsenic in ambient air generally range from 1 to 3 nanograms per cubic meter (ng/m^3), but concentrations in an urban area may range up to 100 ng/m^3. Seawater typically contains 1.5 – 1.7 ppb total arsenic (EFSA, 2009). Arsenic concentrations in natural surface and groundwater of the United States are generally less than the EPA Maximum Contaminant Level (MCL) of 10 ppb, but may exceed this level in private wells, contaminated areas or areas with high soil levels of arsenic (ATSDR, 2007). Tap water in the United States contains, on average, 2 ppb total arsenic, considering all sources of water; i.e., municipal water supplies as well as surface and groundwater sources (ATSDR, 2007). The primary forms of arsenic found in drinking water are forms of inorganic arsenic; arsenite (As^{III}) and arsenate

(As^V). Naturally occurring arsenic-contaminated groundwater has severely affected people in Holocene sediment flood-plain regions of Southeast Asia, most notably the Bengal Delta, and in certain arid regions, such as Inner Mongolia, China, and the Atacama Desert (Chile), where people have been chronically exposed to elevated arsenic in drinking water (ATSDR, 2007; EFSA, 2009; JECFA, 2011).

The background soil content of arsenic varies widely, typically ranging from one to 40 parts per million (ppm), with an average of 7.2 ppm (ATSDR, 2007). Arsenic is taken up by plants through pathways for nutrients. Compared with other cereals, such as wheat and barley, rice has, in general, a much higher arsenic concentration. This is due to rice being the only major cereal crop grown under flooded conditions. This leads to high arsenic availability by causing the reduction of immobile arsenate in non-flooded soils to the more mobile arsenite. This leads to both arsenate and arsenite building up in high concentrations close to the root. Both arsenate and arsenite are analogs of the plant micronutrients phosphate and silicic acid, and plants have evolved efficient mechanisms of capturing them from soil solution. (Zhao *et al.*, 2010).

The highest levels of total arsenic in food are generally found in fish, crustaceans, and seaweed, where the arsenic occurs primarily in organic forms, such as arsenobetaine and arsenocholine, and arsenosugars, which have been considered to be of little toxicological concern (ATSDR, 2007). FDA's TDS measured total arsenic in a variety of foods. Excluding seafood, the highest mean levels of total arsenic among the foods analyzed for the TDS are in rice grain and rice products (e.g., rice cereal) (see Appendix 9.1). Other potential sources of arsenic exposure include fruit juices, fruits, meats, vegetables, beer, wine, flour, corn, and wheat (Xue *et al.*, 2010) as well as drinking water.

Inorganic arsenic can be metabolized to organic arsenic. Two organic forms that are of toxicological concern, monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V), can also be found in various types of finfish, crabs, and mollusks. Arsenosugars are the major species detected in seaweed and are also found, to a lesser extent, in marine mollusks. Small amounts of MMA^V and DMA^V are also found in some vegetables and fruit juices (ATSDR, 2007; EFSA, 2009; JECFA, 2011). MMA is present in only trace amounts in rice grain, if at all. DMA is the dominant organic species of arsenic in rice grain (Meharg and Zhao, 2012).

2.1.2 ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Inorganic arsenic

Soluble inorganic arsenic is highly bioavailable and is rapidly absorbed in biological systems. It is rapidly cleared from blood in humans and in some animals. Once absorbed, inorganic arsenic is metabolized by reduction from As^V to As^{III} in the blood and is taken up by cells in tissues,

mainly the liver, followed by intracellular oxidative addition of methyl groups to form MMA^V and DMA^V. During the methylation process, MMA and DMA may exist in both trivalent and pentavalent oxidation states. Evidence has shown that trivalent forms of arsenic including arsenic, MMA^{III}, and DMA^{III} are more toxic than the pentavalent forms (NRC, 2001; NRC, 2013). MMA^{III}, the first methylation metabolite of inorganic arsenic, may be more cytotoxic than inorganic as shown in *in vitro* studies (Styblo *et al.*, 2000). Alternative pathways include the production of methylated arsenical glutathione metabolites, a process that also occurs in the liver. Arsenite (As^{III}) is taken up into cells more extensively than arsenate (As^V). Arsenite is also a preferred substrate for arsenite methyltransferase (As3MT) over arsenate, and thus is metabolized more extensively than arsenate.

Two basic processes are involved in the metabolism of inorganic arsenic: 1) reduction/oxidation reactions that interconvert As^{III} and As^V and 2) methylation reactions that convert arsenite (As^{III}) to MMA and DMA, although there is uncertainty as to the metabolic pathway (Sams II *et al.*, 2007; Hayakawa *et al.*, 2005). Two possible mechanisms have been proposed for the metabolic pathway of inorganic arsenic: the classical oxidative methylation pathway and the reductive methylation pathway (glutathione conjugation pathway). The classical oxidation methylation pathway involves a series of reduction and oxidative methylations, in which adding the methyl group to the trivalent arsenic by As3MT occurs together with the oxidation to the pentavalent arsenic species.The reductive methylation pathway involves the conjugation of trivalent arsenic with glutathione first before As3MT methylation, followed by the oxidation to the pentavalent arsenic species (Watanabe and Hirano, 2013). A third methylation pathway was proposed (Dheeman *et al.*, 2014) which shows that the products of As3MT methylation are the trivalent methylated arsenic species and that the oxidation and the reduction of arsenic occur as enzyme-bound intermediates. Watanabe and Hirano (2013) have reviewed and provided a detailed discussion of the metabolism of inorganic arsenic and the toxicity of its metabolites, MMA and DMA, in mammals. Methylation reactions facilitate the excretion of inorganic arsenic from the body as both MMA and DMA, which are readily excreted in urine. The methylation process is not entirely complete and some ingested inorganic arsenic can also be excreted directly in the urine. In contrast, with the exception of arsenosugars, ingested organic arsenicals, such as MMA, DMA, and arsenobetaine, the major form of arsenic in most seafood and fish, do not readily enter the cell, undergo limited metabolism, and are excreted unchanged in the urine (ATSDR, 2007).

In humans, inorganic arsenic is extensively methylated, and its metabolites are excreted primarily in the urine. Ingested inorganic arsenic is excreted via the kidney within a few days as inorganic As^V and As^{III} and as MMA^V and DMA^V, with lesser amounts of the trivalent methylated metabolites MMA^{III} and DMA^{III}. Age, gender and smoking may contribute to the large individual variations in arsenic methylation in humans (EFSA, 2009; ATSDR, 2007). Similar urinary metabolic profiles were reported among family members (Chung *et al.*, 2002).

Other than genetic polymorphisms and wide differences in methyltransferase activities, nutritional status may also influence methylation capacity (ATSDR, 2007; EFSA, 2009). The level of arsenic in urine is commonly used as a measure of recent exposure. Arsenic levels in hair and nails have been shown to provide possible biomarkers for longer-term chronic exposure to arsenic in humans (e.g., several months), provided that external contamination of hair and nails can be ruled out (Marchiset-Ferlay *et al.*, 2012; Lin *et al.*, 1998; Karagas *et al.*, 1996).

By measuring the relative amount of arsenic metabolites in urine, it has been shown that intracellular metabolism of inorganic arsenic involves extensive metabolism to DMA^V and MMA^V in most animal species, including humans. According to a study of the U.S. population, based on NHANES 2003-2004 data, DMA^V is generally the most abundant methylated arsenical in urine, comprising an average of 45% of total arsenic in urine (Caldwell *et al.*, 2009).

Organic Arsenic

Based on urinary excretion data, ingested MMA and DMA are well absorbed (at least 75 – 85%) from the gastrointestinal (GI) tract in several species, including humans (ATSDR, 2007). We know of no studies of the distribution of orally ingested MMA or DMA in humans. Studies in other animals have shown that MMA and DMA are distributed to all tissues after acute oral doses. In mice, MMA rapidly distributes throughout the body, with peak concentrations largest in the bladder and concentrations in kidneys and lungs larger than those in the blood (ATSDR, 2007). However, in contrast to ingested inorganic arsenic, which undergoes extensive intracellular metabolism to DMA, ingested organic arsenicals undergo limited intracellular metabolism, with the exception of arsenosugars, which may undergo extensive metabolism.

2.2 HEALTH EFFECTS OF INORGANIC ARSENIC

2.2.1 PROPOSED MECHANISMS OF ACTION

Although chronic exposure to inorganic arsenic in drinking-water has been associated with cancers in humans, the exact molecular mechanisms are not clear. Several modes of action of inorganic arsenic in carcinogenesis have been proposed, including induction of oxidative stress; genotoxicity, as induction of mutations and chromosomal aberrations; modulation of signal transduction and apoptosis (growth factors, cell proliferation, and promotion); and alterations in gene expressions via hyper- and hypomethylation of DNA.

In studies of rodent models either DMA or arsenate and arsenite administered to rats and mice in the diet or in drinking-water induced cytotoxicity and necrosis of the urothelial superficial layer and hyperplasia in the urinary bladder of the animals. The authors postulate that arsenic-induced

bladder cancer is a non-linear process involving urothelial cytotoxicity and regenerative proliferation (Suzuki *et al.*, 2008; Cohen *et al.*, 2007; Arnold *et al.*, 2013; Suzuki *et al.*, 2010). It is noteworthy that although inorganic arsenic and DMA induce similar urothelial lesions in rats and mice, only DMA is a rodent urinary bladder carcinogen, and then only in rats, despite robust testing in both species (Arnold *et al.*, 2006). This generates potential questions concerning the applicability of this regenerative hyperplasia postulate to species other than rats. Because of the differences in the metabolism, pharmacokinetics, and toxicity of arsenic across species, it is unknown if findings in rodent studies can be directly applied to humans. Evidence suggests that arsenic activates Hedgehog signaling, a signaling pathway that transmits information to cells for proper development; malfunctions of this pathway have been implicated in some cancers (Fei *et al.*, 2010). The pathway is named after genes called Hedgehog genes that are involved in the signaling pathway and are present in many animals, including humans. These authors also show a strong positive correlation between arsenic exposure and high levels of Hedgehog activity in tumor samples from a cohort of bladder-cancer patients. Arsenic activates numerous other pathways relevant to cancer in a variety of target cell models.

Another study evaluated gene-expression changes in a small number of cultured human primary uroepithelial cells treated with mixtures of inorganic arsenic and its metabolites. This study indicates changes in other key signaling pathways, such as those involved in oxidative stress, protein folding, growth regulation, metallothionein regulation, DNA damage sensing, thioredoxin regulation, and immune response (Yager *et al.*, 2013). Inorganic arsenic does not directly react with DNA. However, inorganic arsenic has been shown, in both *in vitro* and *in vivo* studies, to break chromosomes and cause extensive damage to DNA in a variety of human tissues. For more information on this indirect mode of action, see Nesnow *et al.* (2002).

The Health Effects of Arsenic Longitudinal Study (HEALS) is a prospective cohort study of increased overall mortality and chronic-disease mortality associated with arsenic in drinking water in the Araihazar region of Bangladesh, from which findings have been published. The HEALS cohort includes concentrations at the low end of the dose-response curve and concentrations at the high end at which known health effects occur. The authors reported a dose-related trend in mortality with exposure to increasing concentrations, with no apparent threshold (Argos, *et al.*, 2010). However, while the study data appeared to support a dose-related trend in mortality, the only statistically significant increase in mortality was recorded at levels above 150 ppb. Thus, as discussed in a paper by EPA scientists (Kitchin and Conolly, 2010), there are multiple possible mechanisms underlying the carcinogenic effects of inorganic arsenic. These include the genotoxicity and clastogenicity of organic and inorganic arsenicals that may warrant linear extrapolation, as well as other mechanisms, such as oxidative stress and epigenetic effects that may exhibit nonlinear characteristics (Kitchin and Conolly, 2010).

It is probable that more than one mechanism of action is involved in the carcinogenicity of inorganic arsenic. The delay between exposure and increased incidence of lung and bladder

cancer in Chile (Marshall *et al*., 2007, Steinmaus *et al*., 2014) makes it clear that at least some of the mechanisms occur at early stages of carcinogenesis. The modes of action of arsenic in lung and bladder carcinogenesis are not completely understood, but some patterns appear to be emerging. Although arsenic is not directly mutagenic, it has been shown to affect several oncogenic processes that are relevant to cancer, including epigenetic, microRNA, gene expression, and mitochondrial DNA alterations (NRC, 2013). This is an area of active research that FDA continues to monitor, in collaboration with other federal agencies.

2.2.2 SHORT-TERM AND INTERMEDIATE EXPOSURE

Ingestion of large doses of arsenic can result in death (ATSDR, 2007). The oral lethal dose of arsenic trioxide was reported to be between 70 and 180 mg/day. The estimated minimum lethal dose in humans ranges from 1 to 3 mg per kg of body weight per day (mg As/kg bw/day). Poisoning may appear with daily doses of inorganic arsenic as low as a few milligrams for a short period of time; e.g., weeks. For example, more than 200 adults with an estimated daily exposure of 3 mg of arsenic for 2 to 3 weeks were poisoned by contaminated soy sauce. This equates to a dose of 0.05 mg/kg bw/day (ATSDR, 2007). Depending on dose and duration of exposure, adverse health effects caused by inorganic arsenic can occur in many organs. Symptoms (e.g. diarrhea, vomiting, blood in the urine, muscle cramps, stomach pain, and convulsions) of acute exposure to arsenic in drinking water, at doses of 0.2 mg/kg bw/day or above, usually occur within the first several hours.

Exposure to elevated arsenic in drinking water, for an intermediate period of time (e.g., weeks to months), can result in gastrointestinal effects, such as abdominal pain, vomiting, diarrhea, and muscular cramping; hematological effects, such as anemia and leucopenia; and peripheral neuropathy, such as numbness, burning, or tingling sensations or pain in the extremities. Metallic taste, garlic odor in breath and feces, and salivation may also be present (ATSDR, 2007).

2.2.3 CHRONIC EXPOSURE

One of the first signs of chronic exposure to arsenic is specific dermal effects. Diffuse or spotted hyperpigmentation followed by palmer-plantar hyperkeratosis after 6 months to 3 years of ingestion of high doses of arsenic (0.04 mg/kg bw/day) or 5 to 15 years of ingestion of low doses of arsenic (0.01 mg/kg bw/day or higher) (NRC, 2001; ATSDR, 2007; EFSA, 2009). Chronic exposure to 0.02 mg/kg bw/day or higher has been shown to cause skin lesions and other health outcomes, including peripheral vascular effects, cardiovascular effects, diabetes mellitus, peripheral neuropathy, diseases of the respiratory system, and cancers (skin and internal organs; ATSDR, 2007; EFSA, 2009; IARC, 2012).

2.2.4 EPIDEMIOLOGICAL STUDIES

The main adverse effects reported to be associated with long-term ingestion of inorganic arsenic in humans are cancer, skin lesions, cardiovascular disease, neurodevelopmental toxicity, adverse pregnancy outcomes, non-malignant lung disease, and diabetes (NRC, 2013). Of these, the greatest strength of evidence for a causal association is for cancers of the skin, bladder, and lung,for skin lesions, and for ischemic heart disease (NRC, 2013

The major source of evidence for human carcinogenicity of inorganic arsenic comes from ecological, case-control, and prospective studies on the impact of arsenic in drinking water. These studies have been conducted in many areas of the world where exposure from drinking-water greatly exceeds exposure from dietary sources, including Taiwan, Northern Chile, Argentina, and Bangladesh, where the range of drinking-water concentrations exceeded 100 ppb. A population-based, case-control study in northern Chile clearly showed an increased incidence of bladder and lung cancer associated with long-term drinking-water arsenic concentrations of 91 – 335 µg/L or greater, but not at 11 – 90 µg/L, as compared with controls exposed to fewer than 11 µg/L (Steinmaus *et al.*, 2013). This study also provides data on long-term individual exposure to arsenic via drinking-water and the first evidence of a long latency of arsenic-related cancers in humans due to high exposure to arsenic. This study showed that higher exposure to arsenic (860 µg/L) in drinking water was associated with risk of lung and bladder cancer 4 to 7 times higher than that from lower exposure, even after exposure was stopped for an average of 38 years.

Two detailed reviews of the epidemiological literature have been published by JECFA (2011) and IARC (2012). The tumor types most often associated with arsenic exposure are lung cancer, bladder cancer, and skin cancer. The strongest evidence for lung cancer has come from studies in southwestern Taiwan (Chen *et al.*, 1985, 1988; Wu *et al.*, 1989; Chen and Wang, 1990; Tsai *et al.*, 1999), northwestern Taiwan (Chen *et al.*, 2010a), Chile (Marshall *et al.*, 2007), and Bangladesh (Mostafa *et al.*, 2008). Evidence for bladder cancer has come from studies in southwestern Taiwan (Chen *et al.*, 1985, 1988; Wu *et al.*, 1989; Chen and Wang, 1990; Tsai *et al.*, 1999), northwestern Taiwan (Chen *et al.*, 2010b), Chile (Marshall *et al.*, 2007), and Argentina (Hopenhayn-Rich *et al.*, 1996, 1998). Skin cancer has been associated with higher levels of inorganic arsenic in drinking water (> 300 ppb), with the primary evidence coming from southwestern Taiwan (Tseng *et al.*, 1968; Chen *et al.*, 1985, 1988; Wu *et al.*, 1989) and Chile (Smith *et al.*, 1998).

Numerous epidemiological studies have reported the association between methylation capacity (specifically, high percentage of urinary MMA) and arsenic-related health effects, including cancers. Both genetic and environmental factors can influence or regulate arsenic methylation and, thus, susceptibility to arsenic-associated disease in humans. An indication of increased lung-cancer risk was reported in subjects who had high urinary percentages of MMA and carried a

specific variant of the cystathione beta-synthase gene, a folate-metabolizing gene (Steinmaus *et al.*, 2010).

2.3 HEALTH EFFECTS OF MMA AND DMA

2.3.1 TOXICITY OF ORGANIC SPECIES

The studies discussed below examined the effects of exogenous DMA and MMA (not DMA and/or MMA as metabolites of ingested inorganic arsenic).Studies of DMA^V oral exposure in experimental animals have found effects on the urinary bladder, kidneys, thyroid, and fetal development (EFSA, 2009; EPA, 2013a). DMA^V (50 mg/L or more in drinking water or 100 ppm in the diet) has been found to be carcinogenic for the urinary bladder of male and female rats (Wei *et al.*, 2002; Arnold *et al.*, 2006), but not in the urinary bladder of male and female mice fed up to 500 ppm in the diet (equivalent to 94 mg/kg bw/day; Arnold *et al.*, 2006). EPA (2013a) concluded that the mode of action for DMA-induced bladder tumors involves cytotoxicity and sustained increased cell proliferation.

A short-term study showed that DMA^{III} induced slight increases in urothelial cytotoxicity and regenerative proliferation in female C57BL/6 mice when administered at 77.3 ppm, in drinking-water, for 4 weeks, suggesting that DMA^{III} may play a role in pre-neoplastic changes and carcinogenic effects induced by inorganic arsenic (Dodmane *et al.*, 2013).

The gastrointestinal tract, particularly the large intestine, is the primary target organ of MMA following oral exposure. Effects such as histopathology of the cecum, rectum, and/or colon were reported as the most sensitive effects in rat studies of chronic exposure (EPA, 2013a). In studies of chronic exposure, oral administration of MMA^V to experimental animals was shown to have effects on the gastrointestinal tract, kidney, thyroid, and reproductive system, with the effect seen at the lowest doses being diarrhea (ATSDR, 2007). MMA^V was not carcinogenic in 2-year bioassays when given to male rats at up to 200 mg/L in drinking water or when given to male and female mice or rats at up to 400 mg/kg in the diet (Arnold *et al.*, 2003; Shen *et al.*, 2003).

IARC (2012) concluded that there is inadequate evidence in experimental animals to determine the carcinogenicity of MMA^V. EPA (2013a) classified MMA as a "not likely" human carcinogen and concluded that it is not mutagenic or genotoxic.

Little information exists on early-life toxicity of DMA^V or MMA^V. Developmental toxicity studies of orally administered DMA^V and MMA^V in the Sprague-Dawley rat and New Zealand white rabbit have shown an absence of dose-related effects at exposure levels that were not toxic in the pregnant animal. Based on pregnancy outcome, the "no observed adverse effect levels"

(NOAELs) for developmental toxicity of orally administered MMA^V were 100 and 7 mg/kg bw/day in the rat and rabbit, respectively, and for DMA^V were 12 mg/kg/day in both species. Maternal and fetal toxicity were observed in rats and rabbits at doses of MMA^V of 500 and 12 mg/kg bw/day, respectively, and at doses of DMA^V of 36 and 48 mg/kg bw/day, respectively (Irvine *et al.*, 2006).

Two studies examined the effects of transplacental exposures on adult offspring. In the first study, pregnant CD1 mice were given drinking water containing up to 25 ppm MMA^{III}, and tumors were observed in the offspring up to 2 years of age. Female offspring exhibited dose-related increases in total epithelial uterine tumors, oviduct hyperplasia, adrenal cortical adenoma, and total epithelial ovarian tumors. Male offspring showed dose-related increases in hepatocellular carcinoma, adrenal adenoma, lung adenocarcinoma, and unusual testicular lesions (Tokar *et al.*, 2012a). The second study examined tumor incidence in male offspring exposed prenatally to inorganic arsenic (85 ppm in maternal drinking water), followed by 200 ppm DMA^V drinking-water exposure through adulthood. DMA^V alone did not induce renal tumors or renal hyperplasia, but did induce urinary bladder hyperplasia, lung adenocarcinomas, and adrenal adenomas. Prenatal arsenic plus DMA^V caused a significant increase in renal tumors, renal hyperplasia, urinary bladder hyperplasia, hepatocellular carcinoma, lung adenocarcinomas, and adrenal adenomas (Tokar *et al.*, 2012b).

DMA^V and MMA^V did not result in clinical signs of neurotoxicity or brain lesions in rats or mice after chronic dietary exposures (ATSDR, 2007). In these studies, rats were exposed to DMA at 7.8 mg/kg/day or to MMA at 72.4 mg/kg and mice were exposed to DMA at 94 mg/kg/day or to MMA at 67.1 mg/kg/day. These doses are markedly higher than those commonly seen in humans.

2.4 EFFECTS OF EARLY-LIFE EXPOSURE TO ARSENIC

The toxic effects of chronic arsenic exposure have been mainly associated with studies of health effects in adults due, in part, to the limitations of conducting studies using children as test subjects and, in part, due to the difficulties in measuring developmental deficient endpoints in young subjects. There is evidence that increased cancer in adults may occur as a result of exposure during childhood. In particular, an ecological study of a Chilean cohort exposed to elevated levels of arsenic over a 12-year period early in life reported an increase in lung and bladder cancer that peaked 25 years after the elevated exposure had stopped (Marshall *et al.*, 2007).

Some initial pharmacokinetic studies indicated that children may metabolize arsenic at a slower rate than do adults (ATSDR, 2007). Other studies have found that the arsenic methylation may be more efficient in children than in adults. For example, Lindberg *et al.* (2008) found a 30% variation in arsenic metabolism of test subjects due to gender, age and exposure level. Furthermore, after adjustment of the dose for body weight, children may be expected to exhibit the same dose-response relationship for acute and short-term chronic effects as adults exhibit. The temporal evidence from episodic exposures (e.g., Marshall *et al.*, 2007; Steinmaus *et al.*, 2013) indicates that exposures earlier in life are likely to be more important than exposures later in life for the development of cancer.

See Section 2.6 for a detailed discussion on non-cancer health effects from arsenic exposure during pregnancy, infancy, and early childhood. See Appendix 9.15 for a discussion and update to the pertinent literature on the adverse effects of inorganic arsenic exposure on cancer endpoints in all exposed populations from October 2013 through February 2015.

2.5 LUNG AND BLADDER CANCER: BACKGROUND INCIDENCE, LIFETIME RISK, AND RISK FACTORS IN THE U.S.

This section provides general information about lung and bladder cancer incidence, including information about known risk factors other than arsenic. Lung cancer is of significant public-health concern, due to its high incidence and high mortality. The National Cancer Institute (NCI) of the U.S. National Institutes of Health estimated that there would be 221,200 new lung- cancer cases in 2015 (representing 13.3% of all new cancer cases) and 158,040 deaths (representing 26.8% of all cancer deaths). Based on data from 2005 - 2011, the 5-year survival after diagnosis is 17.4%. The lifetime risk of lung cancer in men and women in the U.S. is approximately 6.6% (NCI, 2015a). Lung cancer is also highly significant from the standpoint of lost years of life. NCI cancer statistics indicate that a total of 2,393,100 person-years of life were lost due to lung and bronchus cancer in 2012, the highest total for all cancers. This was three times higher than the total person-years of life lost for colon and rectum cancer, which had the second-highest total person-years of life lost among all cancers. The average years of life lost, per person, from lung and bronchus cancer is 15.2 years (NCI, 2015b).

Most lung cancers are due to cigarette smoking (NCI, 2015c). However, 10 – 15% of lung cancers occur in never-smokers (Samet *et al.*, 2009). In addition to environmental arsenic exposure, other known risk factors for lung cancer include exposure to secondhand tobacco smoke; having a family history of lung cancer; ionizing radiation (from radiation therapy to the breast or chest and environmental radon exposure in buildings); occupational exposure to asbestos, silica, arsenic, nickel, or chromium; air pollution; and previous lung diseases, including

chronic obstructive pulmonary disease, pneumonia, and tuberculosis (NCI, 2015c; Sisti and Boffetta, 2012).

Compared with the U.S. incidence of lung cancer, the U.S. incidence of bladder cancer and its mortality is lower. NCI estimated that there would be 74,000 new bladder cancer cases in 2015 (representing 4.5% of all new cancer cases) and 16,000 deaths (representing 2.7% of all cancer deaths). Based on data from 2005 - 2011, the 5-year survival after diagnosis is 77.4%. The lifetime risk of bladder cancer in U.S. men and women is approximately 2.4% (NCI, 2015d). NCI cancer statistics for 2012 indicate a total of 173,100 person-years of life lost due to bladder cancer. The average years of life lost per person for urinary bladder cancer is 11.4 years (NCI, 2015b). Cigarette smoking is the most important known cause of bladder cancer (NCI, 2015d). A study found a population-attributable risk of bladder cancer from tobacco smoking of approximately 50% in men and women (Freedman *et al.*, 2011). Specific occupational exposures are considered to be the second-most important cause of bladder cancer in both men and women, with some studies suggesting that certain high-risk occupations may be responsible for 4% to 10% of bladder cancers in men and a lower percentage in women; aromatic amines, polycyclic aromatic hydrocarbons (PAHs), and diesel engine exhaust are the exposures most consistently found to increase the risk (Kogevinas *et al.*, 2008). In addition to environmental arsenic exposure, other risk factors for bladder cancer include; for example, inflammation of the bladder (either by stones or infection), ionizing radiation, and chlorination by-products in drinking water (Kogevinas *et al.*, 2008).

2.6 NON-CANCER HEALTH EFFECTS DURING PREGNANCY (EFFECTS ON FETUS), INFANCY, AND EARLY CHILDHOOD

There is a growing body of evidence that exposure to inorganic arsenic contributes to the development of many non-cancer adverse health effects and that risk assessments for inorganic arsenic might well involve separate assessments for the general population and for susceptible life stages, especially for non-cancer health effects.

The NRC (2013) report on inorganic arsenic lists a hierarchy of Health Endpoints of Concern for inorganic arsenic. These endpoints were listed by Tiers - Tier 1 was evidence of a causal association determined by other agencies and/or published systematic reviews, Tier 2 were other priority outcomes, and Tier 3 were other endpoints to consider. For this risk assessment, we focused on two endpoints of concern in the NRC report (2013) – adverse pregnancy outcomes and neurodevelopment. Neurodevelopmental toxicity was listed under Tier 2 and adverse pregnancy outcomes was listed as Tier 2 for infant morbidity, and Tier 3 for fetal loss, stillbirth, and neonatal mortality. We focused on these endpoints for two reasons. The first was because there is strong scientific evidence that pregnancy and early childhood are “windows of

susceptibility" to the toxic effects of metals (Wright and Baccarelli, 2007). The second reason was because FDA's sampling of infant rice cereal, a commodity that often makes up the majority of an infant's diet, was demonstrated to have high (average = 120 ppb) levels of inorganic arsenic (FDA, 2013; see Table 9.14 in Appendix 9.5).

The NRC report states that "consideration should be given to the growing evidence from human and animal studies that suggests that early life exposure to arsenic may increase the risk of adverse health effects and the risk of impaired development in infancy and childhood and later in life." (NRC, 2013). Arsenic easily crosses the placenta (Concha *et al.*, 1998), and even moderate exposure to arsenic during pregnancy has been associated with adverse health outcomes in the fetus (Rahman *et al.*, 2009). Inorganic arsenic is found at low levels in breast milk; thus, exposure is thought to be low for solely breast-fed infants (EFSA, 2009).

Young children (< 4 years), on a per-body-mass basis, have about 3-fold greater food intakes, compared with adults, leading to greater dietary exposure to inorganic arsenic (EFSA, 2009). Children also generally have a less-varied diet than do adults. Thus, elevated levels of inorganic arsenic in food or liquids that children eat, such as rice products, may represent a significant source of exposure for children (ATSDR, 2007; EFSA, 2009). FDA's sampling of rice products showed levels of 105 ppb and 120 ppb of inorganic arsenic in infant white rice cereal and infant brown rice cereal, respectively (FDA, 2013 and 2015).

The evidence of cancer risk posed by inorganic arsenic is well supported by numerous epidemiology studies and previous assessments (ATSDR, 2007; EFSA, 2009; JECFA, 2011; IARC, 2012; NRC, 2013). However, in 2013 when we initiated this risk assessment, we found no reviews of the literature regarding adverse health effects during pregnancy, infancy, or early childhood. Much of the scientific data on such effects during these life stages were published within the last few years, and therefore were not included in the ATSDR (2007) or EFSA (2009) assessments of inorganic arsenic and were not included in the calculated ATSDR Minimal Residue Limits (MRLs) or U.S. EPA Reference Doses.

In reviewing the literature, FDA chose to use the approach and the causality framework developed by the EPA IRIS program for its current review of inorganic arsenic and which was presented to the NRC for review. We adopted the same approach as EPA for our causality assessment of inorganic arsenic in susceptible populations because it outlined a scientifically defensible approach and assured concordance of methodology between the two federal agencies. The EPA's causal determination framework categorizes the evidence on the different endpoints into five possible categories: causal relationship, likely to be a causal relationship, suggestive of a causal relationship, inadequate to infer a causal relationship, and not likely to be a causal relationship. For a detailed explanation of the criteria for each category, see the Causal Framework Table in Appendix 9.14.

The question addressed by this literature review was whether pregnancy, infancy, and/or early childhood are periods of greater susceptibility to the toxic effects of oral inorganic arsenic exposure and, if so, can these risks be quantified.

Electronic citation databases available to the FDA (including PubMed, Web of Science, and Toxline) were searched for peer-reviewed studies that examined the effects of oral exposure to inorganic arsenic during pregnancy, infancy, and early childhood. Only data from the original research papers were considered. Papers consisting of reviews of research conducted by other investigators were not included. For this review, we considered only published literature studies conducted in humans, but did not include a review of toxicity effects seen in animal models. Inorganic arsenic has been shown to be embryotoxic and teratogenic in animal studies. However, because experimental animals differ considerably from humans with regard to arsenic metabolism and other aspects of toxicokinetics, the results of toxicity studies in animals do not provide a suitable basis for risk characterization. Details of the available animal studies can be found in the 2007 ATSDR, 2009 EFSA, and 2012 IARC reports on arsenic.

In conducting this review we made the following assumptions.

- Inorganic arsenic was considered the primary stressor for risk. Organic metabolites may play a role in exacerbating the effects of exposure but are unlikely to have unique toxicities.
- Review focused on the effects of inorganic arsenic exposure by the oral route only.
- Review focused on lifestage susceptibility – *in utero* and early childhood (ages 0 – 6 years)
- Review considered the health effects reported in epidemiology studies regardless of the geographic location of the human population studied
- Review will consider those epidemiology studies with no known mode of action data to humans.
- Health effects that are considered causal or likely causal by two independent reviewers were included in the assessment.
- The reference population was the U.S. population.

We excluded from consideration, the following.

- Data from review articles.
- Data from studies that are not in peer-reviewed journals, including abstracts (identified based on a single page reference), letters, comments, and editorials
- Data from in vitro research studies.
- Data from studies where exposure is not from the oral route.
- Data from studies of populations living near environmental exposure sites such as smelters or Superfund sites where exposure may, at least in part, be due to the non-oral route and where there is likely to be other toxic exposures.

- Data on exposure from oral consumption of soils by children, although this is an acknowledged route of oral exposure for children.
- Studies that describe the impact of arsenic on non-mammalian animal models (e.g., fish) or plant life.
- Data from studies where arsenic exposure was not the primary focus of the research, i.e., arsenic may be considered a confounder for research involving other chemicals.

To mimize the risk of bias in this assessment, we used a two-reviewer process. The first reviewer read the papers and extracted data, and then considered the extracted data to address key questions for the risk of bias questions. The secondary reviewer considered the extracted data but was blinded to the conclusions of the first reviewer. The overall goal was to determine if both reviewers agree, and if not, to discuss their differences and determine mutually-acceptable conclusions. Additionally, the second reviewer verified that all relevant information was considered and clearly described in the first reviewer's analysis.

For each paper reviewed, we considered the following questions based upon Bradford Hill criteria (Hill, 1965; Schunemann *et al.*, 2011):

- Does exposure precede outcome?
- Were standard definitions used across all the studies?
- Were dose-response relationships seen?
- Was the pattern of evidence consistent across studies?
- Were the comparison groups appropriate?
- Did attrition affect the results?
- Did the studies account for important confounders?
- Were biologically plausible explanations given?

2.6.1 EFFECTS OF ARSENIC ON FETAL DEVELOPMENT DURING PREGNANCY

Several epidemiology studies have been conducted to determine the association between inorganic arsenic exposure and adverse pregnancy outcomes in different areas of the world. In many areas, the main source of water for drinking and cooking is tube wells, in which arsenic levels can be greater than 100 µg/L. A tube well is an easily-installed, simple type of well that is most commonly used in developing nations. Arsenic exposure was assessed by different methodologies in these studies, including analysis of total arsenic and/or arsenic species and of arsenic in maternal urine collected at various stages of pregnancy, or by looking at the average and/or range of arsenic levels in tube wells available to the populations studied. Pregnancy outcomes that were addressed included stillbirths, spontaneous abortion, low birth size at term, infectious-disease susceptibility, and pre-term birth. See Appendix 9.13 for a synopsis of the studies we considered in our assessment.

Using the Bradford Hill criteria described above, for each paper considered we determined that:

- Standard definitions for each of the outcomes were used across all studies.
- In each study considered, exposure always preceded the outcome.
- Dose-response relationships were seen in some of the studies.
- The pattern of evidence related to the potential impacts was consistent across studies.
- Comparison groups were appropriate, and the use of a small number of districts from which to draw subjects ensured that the population was homogenous, compared with data gathered at the state or country level.
- Attrition did not appear to affect the results; in most studies, there was little movement into or out of districts.
- Each study accounted for important potential confounding and modifying variables, to the best extent possible.
- Biologically plausible explanations for the results were given. Inorganic arsenic has been shown to be a potent toxicant. It readily crosses the placenta and has been measured in fetal cord blood. Fetal growth is influenced by multiple factors, including genetic predisposition, maternal nutrition, and environmental exposures. The mechanisms by which arsenic might affect birth size and other adverse pregnancy outcomes are not well understood (Ahmed *et al.*, 2011).

The major shortcoming in most of the studies was the exposure estimation. Many of the studies used ecological measurements of arsenic exposure by averaging the inorganic arsenic levels in tube wells available to the participants. These data do not account for exposure through food sources, and also do not reflect variation in consumption patterns at the individual level.

Some studies used total arsenic in the urine as a biomarker of exposure. Since these total arsenic levels are usually derived from recent exposure, the values do not take into account fluctuations in exposure over time (i.e. over a person's lifetime). However, the values do take into account exposure from all sources. On the other hand, as urinary arsenic can be high in marine-derived organic arsenic species, such as arsenobetaine, that are relatively benign, total urinary arsenic measurements can be misleading, especially in populations that have access to seafood (Cascio *et*

al., 2011). See Appendix 9.13 for a synopsis of the studies we considered in our assessment, including information on whether total arsenic or inorganic arsenic levels were determined.

The definition for "Likely Causal" from the EPA Framework was as follows: "Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes multiple high-quality studies."

FDA chose this level because it determined that the literature clearly demonstrated a relationship between certain adverse pregnancy outcomes and oral exposure to inorganic arsenic, but important uncertainties remain. That is, not all sources of exposure to inorganic arsenic from the diet were accounted for or quantitated.

Although low-to-moderate levels (50 – 100 µg/L) of maternal intake of inorganic arsenic during pregnancy appear to be associated with adverse health effects in the fetus, the uncertainty in the measurement of exposure to inorganic arsenic in the pregnant women studied along with other weaknesses and confounders in the studies makes difficult the determination of a Tolerable Daily Intake (TDI) for adverse effects during this life stage.

2.6.2 EFFECTS OF ARSENIC DURING INFANCY AND CHILDHOOD

Children are particularly susceptible to neurotoxic effects as a result of even low-level exposure to lead and methyl mercury, and there are data suggesting that children may, likewise, be particularly susceptible to neurotoxic effects of exposure to inorganic arsenic. Children (< 4 years of age) have the highest exposure to inorganic arsenic, because they have 2- to 3-fold higher intakes of food on a per-body-mass basis, compared with those of adults (EFSA, 2009). Because early childhood is a period of rapid brain development, this is an additional reason why this life stage is one of greater susceptibility to neurotoxicants. See Appendix 9.13 for a synopsis of the studies we considered in our assessment.

Using the Bradford Hill criteria described above, for each paper considered we determined the following.

- Standard development and intelligence tests were used in the studies.
- In each study examined, exposure always preceded the outcome.
- Dose-response relationships were seen in some of the studies.
- The pattern of evidence related to the potential impacts was consistent across studies.
- Comparison groups were appropriate, and the use of a small number of districts from which to draw subjects ensured that the population was homogenous, compared with comparison groups from which data are gathered at the state or country level.
- Attrition did not appear to affect the results.
- Each study accounted for important potential confounding and modifying variables, to the best extent possible.
- Biologically plausible explanations for the results were given. Arsenic has been shown to be neurotoxic in both adults and infants accidently exposed to large quantities through their diets.

The major shortcoming in these studies was in the exposure characterization. The studies are not uniform in how they assess exposure. Many of the studies used ecological measurements of arsenic exposure by averaging the inorganic arsenic levels in the tube wells the participants used. These data do not account for exposure through food sources and do not reflect variation at the individual level.

Some studies used total arsenic in the urine as a biomarker of exposure. Since these total arsenic levels are usually derived from recent exposure, the values do not take into account fluctuations in exposure. However, the values do take into account exposure from all sources. On the other hand, as urinary arsenic can be high in marine-derived organic arsenic species, such as arsenobetaine, that are relatively benign, total urinary arsenic measurements can be misleading, especially in populations that have access to seafood (Cascio *et al.*, 2011).

Additionally, these studies measured deficits at one period of time and did not assess the long-term consequences in cognitive function i.e., whether impairments are permanent or are more transitory in nature and whether continued exposure increases the impact. Longitudinal studies are warranted, to evaluate the most critical windows of exposure, the types of effects, and dose-response relationships. However, the studies do support the conclusion that arsenic is associated with neurocognitive deficits in children.

The definition for “Likely Causal” from the EPA Causality Framework is described above. FDA chose “Likely Causal” because we determined that the literature clearly demonstrated a relationship between neurotoxic effects in early childhood and oral exposure to inorganic arsenic, but important uncertainties remain. That is, not all sources of exposure to inorganic arsenic from the diet were accounted for or quantitated, and deficits were measured at a single time point and did not assess the long-term consequences in cognitive function.

Low-to-moderate levels of inorganic arsenic appear to be associated with adverse health effects during childhood. However, there are uncertainties in the data including (1) the measurement of exposure to inorganic arsenic in the children studied, (2) the small number of children studied, and (3) the use of IQ testing not standardized for the population studied, in many cases. We are aware that research is underway, and we are working with EPA in considering any new findings or refined methodological approaches.

For a discussion and update of the pertinent literature on the adverse effects of inorganic arsenic exposure to the developing fetus and to young children, see Appendix 9.15 which summarizes the literature reviewed from October 2013 through February 2015.

3 HAZARD CHARACTERIZATION (DOSE-RESPONSE) FOR LUNG AND BLADDER CANCER

This section provides a description of the data and methodology for the quantitative dose-response model developed for this risk assessment and provides a comparison to other dose-response models in the literature.

3.1 FDA DOSE-RESPONSE MODEL FOR LUNG AND BLADDER CANCER

3.1.1 DATA SELECTION

Our dose-response model largely relies on data and modeling assumptions identified in a report by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JECFA, 2011). A prospective cohort study in northeastern Taiwan was selected by the JECFA committee as the pivotal study for bladder cancer (including all observed urinary tract cancers) (Chen *et al.*, 2010a) and lung cancer (Chen *et al.*, 2010b) risk assessment. Other studies considered by JECFA for risk assessment included earlier studies, with different cohorts, in Taiwan, in which lung and bladder cancer were the primary endpoints (Wu *et al.*, 1989; Chen and Wang, 1990), and studies of skin cancer and other dermal lesions in Bangladesh and China (Ahsan *et al.*, 2006; Rahman *et al.*, 2006; Xia *et al.*, 2009). The U.S. EPA has used some of the former studies (Chen *et al.*, 1988; Wu *et al.*, 1989; Chen *et al.*, 1992) for cancer risk assessments. FDA also considered the Taiwanese studies to be best suited for inorganic arsenic dose-response modeling, because demonstrable (i.e., statistically significant) changes in disease rates were observed at two levels of exposure and because lung and bladder cancer are more serious effects, compared with other health effects; e.g., arsenic-induced skin cancer.

Under a contract with FDA, ORNL conducted a citation-forward literature search for articles published between 2009 and October 2013, to identify any relevant studies not available at the time of the JECFA report (JECFA, 2011) (see Appendix 9.6.1 for a detailed description of the methods, inclusion criteria, and results). From the literature review conducted by ORNL, 18 studies (10 cohort studies, 6 case-control studies, and 2 ecological studies) were identified as candidates for further data analysis. Of these 18, three studies (Fernandez *et al.*, 2012; Hsu *et al.*, 2013b; Wade *et al.*, 2009), in particular, may provide additional information useful for future characterization of the dose-response relationship for inorganic arsenic (see Appendix 9.6.1 and 9.6.2).

3.1.2 ADJUSTING THE DATA FOR USE IN THE FDA DOSE-RESPONSE MODEL

The studies that provided data for our model included data from populations exposed to high or low concentrations of total arsenic in well water. . In total, the Taiwanese cohort began with 8,086 subjects 40 years of age or older who were recruited into the study and had an average of 11.5 years of follow-up. In this cohort design, persons below the age of 40 years were excluded, because lung and bladder cancer incidence is very low in that age group. Total arsenic concentrations in drinking water were available for 6,888 of these subjects. Studies that have speciated arsenic in drinking water in Taiwan have found it to be primarily inorganic arsenic (Lin *et al.*, 1998; Chen *et al.*, 1995). An advantage of the prospective cohort study design is that the cohort is classified in relation to exposure before disease develops. Standardized incidence ratios can also be estimated from this study design, unlike the case-control design, which yields only odds-ratio (OR) estimates.

We addressed the effect of confounding covariates (age, gender, smoking, education level, and alcohol consumption) on bladder and lung cancer cases observed in Chen *et al.* (2010a, 2010b) by using adjusted numbers of cases calculated for each exposure group. To calculate adjusted number of cases for each exposure group, a two-step process was used: (1) the adjusted case frequency was calculated by multiplying the rate in the referent group by the adjusted Relative Risk (RR) value; and (2) the adjusted number of cases was calculated by multiplying the number of subjects in the group by this adjusted case frequency. The resulting adjustment was small, relative to the reported cases (Tables 3.1 and 3.2).

Although prospective epidemiological studies are most suited for dose-response analyses, the studies follow each individual for only a limited period; therefore, results are expressed on a person-year basis. The purpose of our dose-response model was to generate and estimate risk after lifetime exposure; therefore, the incidence rates reported in Chen *et al.* (2010a, 2010b) on a person-year basis were adjusted to estimate lifetime rates. Because cancer rates are dependent on subject age, estimates of lifetime risk accounted for the age of the population by including subject age as one of the variables in the model. This required individual subject data that were not available in the Chen *et al.* (2010a, 2010b) papers. Therefore, an alternative method that reported results for a period of follow-up of 11.5 years (not a complete lifetime) was utilized to estimate lifetime cancer rates for the Chen *et al.* (2010a, 2010b) cohort. This alternative method involved multiplying the observed rates by a factor based on the average life expectancy in Taiwan (76 years[1]), relative to the period of observation (11.5 years), assuming that the disease rate at ages below 40 is negligible.[2] A theoretical maximum value of 3.1 was estimated for the

[1] http://sowf.moi.gov.tw/stat/english/elife/te88210.htm

[2] This assumption is implicit in the study design and is consistent with mortality statistics for lung and bladder cancer in the United States.

Taiwanese cohort, corresponding to the following equation: (76 yr avg Taiwanese lifetime - 40 yr minimum cohort age)/11.5 yr follow-up. However, this method implicitly assumed that the age distribution in the cohort was representative of the general population age 40+. Because the cohort aged during the course of the study, the number of additional cases observed in this closed, aging cohort during the study period was likely to be greater than the one that would have been observed in an open cohort (i.e., with members that were added over time) during the same period of time. Therefore, an uncertainty range spanning from 2 to 3.1 was used as a plausible range. The estimated background cumulative risks (see Table 3.3) were very close to values reported for the referent group (well water < 10 ppb) for this cohort (Yang *et al.*, 2013).

Tables 3.1 and 3.2 provide the data used in our dose-response model for bladder and lung cancer. The bladder-cancer study (Chen *et al.*, 2010a) used for the bladder-cancer model showed a significantly increased trend of relative risk with increasing arsenic concentration in drinking-water when adjusted for age, gender, education level, consumption of well water since birth, and cigarette-smoking and habitual-alcohol-consumption status at the time of enrollment ($P < 0.001$). For exposures above 100 µg/L, relative risks were more than 4, and the lower bound of the relative risk estimates were greater than 1, whereas the relative risks were elevated, but not significantly, for exposures below 100 µg/L. The lung-cancer study (Chen *et al.*, 2010b) also found a significantly increased trend ($P < 0.001$) of lung-cancer risk associated with increasing arsenic concentration in drinking water. However, even though the apparent increase in the number of lung-cancer cases was greater than the number of bladder-cancer cases, the lower bound of the adjusted relative risk for lung cancer was above 1 only at the highest well-water concentration (> 300 µg/L), which may be due to the much-higher background rate of lung cancer.

Table 3.1. Association of Bladder Cancer with Arsenic Exposure in Northeastern Taiwan (in person-years)

Inorganic Arsenic in Water Category range (µg/L)	Inorganic Arsenic Concentration in Well Water[a] (µg/L)	Unadjusted RR[b]	Adjusted RR[b]	*N*	Unadjusted Cases	Adjusted Cases[c]
< 10 (referent group)	2.1	1.00	1.00	2288	5	5.0
10 – 49.9	26.9	1.75	1.66	2093	8	7.6
50 – 99.9	74.6	2.52	2.42	907	5	4.8
100 – 299.9	162.4	4.03	4.13	909	8	8.2
≥ 300	836.3	7.28	7.80	691	11	11.8

[a] Average estimate of the range of inorganic arsenic in drinking-water; values taken from an earlier study on the same cohort (Chiou *et al.*, 2001). Note: The dose-response model used for apple juice (Carrington *et al.*, 2013) estimated the arsenic concentration in water based on estimates provided in JECFA (2011).

[b] The unadjusted RR is the raw relative risk (RR) that is calculated by dividing the number of actual cases by the group size. The adjusted RR is reported in Chen *et al.* (2010a).
[c] Adjusted cases are calculated by multiplying the group size by the adjusted RR.

Table 3.2. Association of Lung Cancer with Arsenic Exposure in Northeastern Taiwan (in person-years)

Inorganic Arsenic in Water Category range (µg/L)	Inorganic Arsenic Concentration in Well Water[a] (µg/L)	Unadjusted RR[b]	Adjusted RR[b]	*N*	Unadjusted Cases	Adjusted Cases[c]
< 10 (referent group)	2.1	1.00	1.00	2288	48	48.0
10 – 49.9	26.9	1.16	1.10	2093	51	48.3
50 – 99.9	74.6	1.05	0.99	907	20	18.8
100 – 299.9	162.4	1.47	1.54	909	28	29.4
≥ 300	836.3	2.14	2.25	691	31	32.6

[a] Average estimate of the range of inorganic arsenic in drinking-water; values taken from an earlier paper on the same cohort (Chiou *et al.*, 2001). Note: The dose-response model used for apple juice (Carrington *et al.*, 2013) estimated the arsenic concentration in water based on estimates provided in JECFA (2011).
[b] The unadjusted RR is the raw relative risk (RR) that is calculated by dividing the number of actual cases by the group size. The adjusted RR is reported in Chen *et al.* (2010a).
[c] Adjusted cases are calculated by multiplying the group size by the adjusted RR.

3.1.3 MODEL METHODOLOGY

Figure 3.1, below, provides a schematic of our dose-response model showing how the adjustments to the epidemiology study data were used in the model. Because of the large uncertainties associated with theoretical approaches to characterizing the dose-response relationship for arsenic-induced cancer, an approach that largely relies on empirical support is appropriate and necessary. A 1,000-iteration bootstrap analysis was used to represent multiple uncertainties associated with the dose-response relationship.

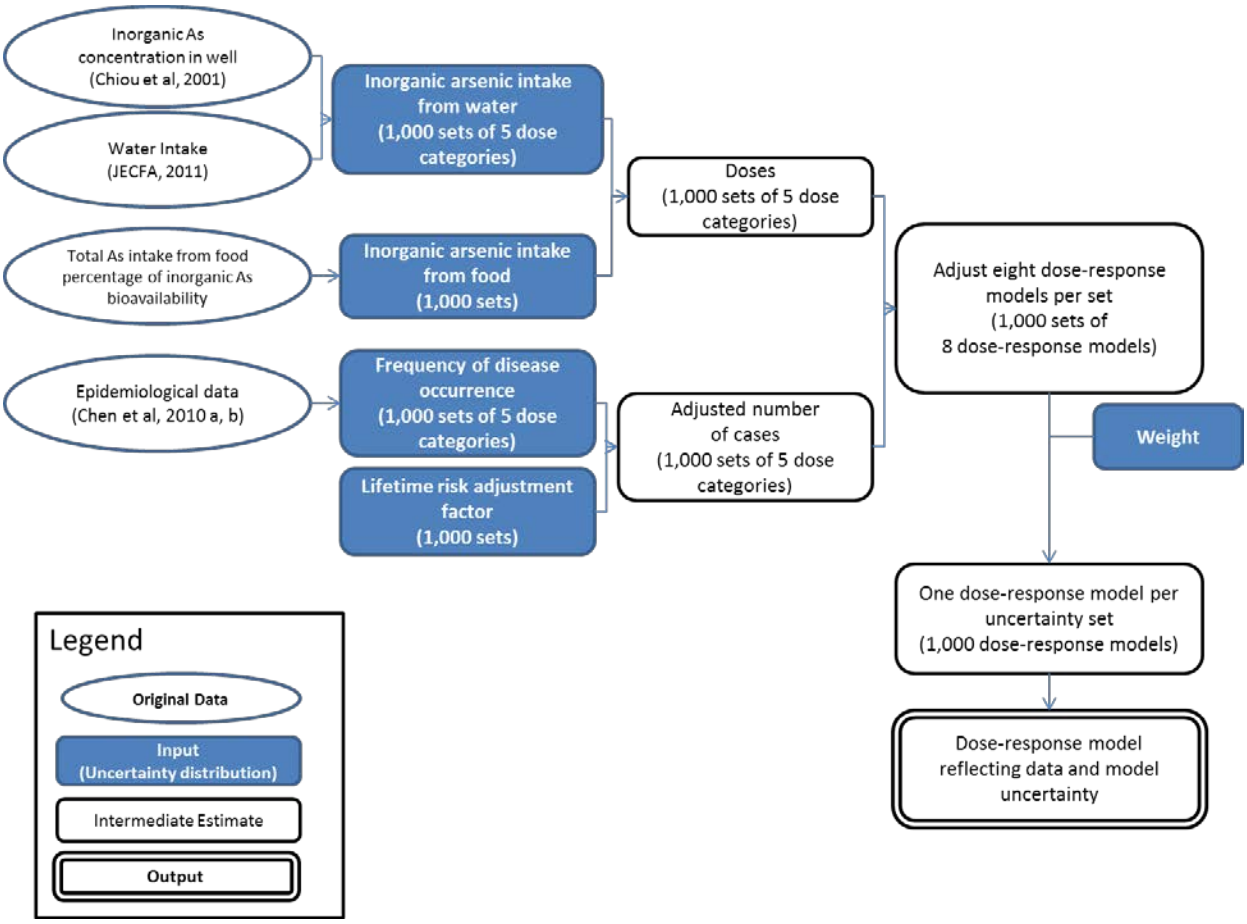

Figure 3.1. FDA Dose-Response Model Structure

3.1.3.1 DOSE-RESPONSE DATA BOOTSTRAPPING

We characterized the uncertainties associated with the Taiwanese data using parametric bootstrapping. Specifically, uncertainty associated with the dose in each of the five groups of exposures was represented by using a range of plausible values for drinking-water consumption (rectangular – a.k.a. uniform – distribution 2 to 4 L/day), for total arsenic intake from food [Pert distribution (Vose, 2008)] with parameters [min=50, mode=68.2, max=200 µg/day (JECFA, 2011)], for the percentage of inorganic arsenic (vs. total arsenic) in food (normal distribution 76 ± 2) from a study on rice, conducted by Liang *et al.* (2010), and for bioavailability (see Section 4.5) of the inorganic arsenic intake from food (rectangular distribution 0.7 to 0.9). A binomial distribution was used to represent uncertainties in the frequency of disease occurrence in the cohort, and a rectangular distribution was used for the lifetime risk adjustment factor (2 to 3.1) (See Section 3.1.2). A 1,000-iteration bootstrap data set reflecting these uncertainties was generated for both lung and bladder cancer; summary statistics are shown in Table 3.3.

Table 3.3. Estimated Doses of Inorganic Arsenic and Lifetime Cancer Rates for Chen Cohort

Category Range (µg/L)	Dose (µg/kg bw/day)	Bladder Cancer Incidence	Lung Cancer Incidence
<10 (referent group)	0.9 (0.7, 1.3)	0.6% (0.3%, 1.2%)	5.4% (4.3%, 6.4%)
10–49.9	2.3 (1.8, 2.9)	1.0% (0.5%, 1.7%)	5.9% (4.7%, 7.0%)
50–99.9	4.9 (3.7, 6.2)	1.6% (0.7%, 2.9%)	5.3% (4.3%, 6.3%)
100–299.9	9.6 (7.1, 12.4)	2.5% (1.3%, 4.3%)	8.3% (6.6%, 9.8%)
≥300	46.0 (32.6, 60.0)	4.5% (2.7%, 7.4%)	12.1% (9.7%, 14.3%)

Note: The values provided are the median and in parenthesis are the 5th and 95th percentiles of the uncertainty distribution (CI90%).

3.1.3.2 MODEL PARAMETER ESTIMATION

Each iteration of the bootstrap data set was modeled with eight different dose-response models: the gamma model, the logistic model, the log-logistic model, the log-probit model, the probit model, the Weibull model, the one-stage model, and the dichotomous Hill model, using maximum-likelihood estimation. Although the bootstrap estimation procedures were carried out using code modified from RIVM Proast (Slob and Cotton, 2012), the resulting parameters were converted to EPA BMDS format for subsequent calculations (see Appendix 9.3). Additional details are given in Appendices 9.2 and 9.3. Because some of the models resulted in virtually identical risk estimates, four redundant models were eliminated. Also, because the dichotomous Hill model ascribed all of the risk to a small subpopulation, it was eliminated for being biologically implausible. For each bootstrap data set, one of the three remaining (Weibull, probit, and log-probit) dose-response models was selected, using a weight of evidence approach that considered goodness of fit and theoretical support (see Appendix 9.4). Sensitivity analyses showing results using a variety of model-weighting approaches, including single model results, are also presented in Appendix 9.4.

3.1.3.3 DIFFERENCES BETWEEN THE PRESENT MODEL AND THE PREVIOUS (2013) VERSION

For this risk assessment, the following improvements were made to the dose-response model used in FDA's 2013 draft risk assessment of arsenic in apple juice (Carrington *et al.*, 2013):

- The values used for inorganic arsenic in drinking water are based on the average measured concentrations reported in Chiou *et al.* (2001), instead of the estimated values used in the JECFA (2011) report (see Tables 3.1 and 3.2).

- Matched random numbers for each Monte Carlo iteration for both bladder and lung cancer were used, so that total cancer incidence for each iteration was estimated using the same dose estimates for each endpoint.

- Parameter estimates were obtained using the maximum-likelihood method, instead of the least-square method.

- A slightly different set of candidate models were used: (1) two models (log-logistic, log-probit) with alternative background parameters were eliminated and (2) a new model (dichotomous Hill), which was added to the EPA BMDS software package in 2011, was included.

- Taiwanese dietary intake estimates from JECFA (2011) were corrected for inorganic arsenic and bioavailability in food. As in the previous assessment, bioavailability from water was assumed to be 100%. See Section 3.1.3.1.

- A number of different approaches to weighting alternative models were explored, and the strategy utilized for the primary estimates was different than in 2013. See the model-weighting description in Appendix 9.4 for additional details and sensitivity analyses that illustrate the impact of model weighting on the estimates.

3.2 OTHER PUBLISHED DOSE-RESPONSE MODELS FOR LUNG AND BLADDER CANCER

3.2.1 U.S. EPA DRINKING-WATER RULE DOSE-RESPONSE MODEL

The cost-benefit analysis that supported the 2001 U.S. EPA Rule for Arsenic in Drinking Water used a dose-response analysis developed under contract for the U.S. EPA Office of Water (Morales *et al.*, 2000). This analysis was based on epidemiological data collected from 42 villages in Southwestern Taiwan (Wu *et al.*, 1989). Although Morales *et al.* (2000) reported the results of the analyses using several different models, the primary model (identified as "Model 1") used by the U.S. EPA cost-benefit analysis was linear, with respect to dose, and used a quadratic function to estimate the influence of age on disease occurrence. The estimated Effective Dose for 1% (ED01) and Lower Bound of the ED01 (LED01) for lung and bladder cancer are given in Table 3.4.

Table 3.4 Linear Slope Estimates and ED01 from Morales *et al.* (2000) Model 1

Endpoint	Sex	ED01 (µg/L)[a]	SEM[b]	Linear Slope[c] (cases per mg/kg bw/day)
Bladder cancer	M	395 (326)	35	0.89 (0.76, 1.02)

Endpoint	Sex	ED01 (µg/L)[a]	SEM[b]	Linear Slope[c] (cases per mg/kg bw/day)
Bladder cancer	F	252 (211)	21	1.39 (1.20, 1.58)
Bladder cancer	M+F	324 (267)	29	1.08 (0.92, 1.24)
Lung cancer	M	364 (294)	36	0.96 (0.81, 1.12)
Lung cancer	F	258 (213)	23	1.36 (1.16, 1.56)
Lung cancer	M+F	311 (252)	30	1.13 (0.95, 1.30)

[a] Effective Dose for 1% (ED01) is equivalent to a BMD1 for a quantal endpoint. The lower bound, equivalent to a $BMDL_{1,}$ is given in parentheses. The values reported in Morales *et al.* (2000) were converted to dietary equivalents using the standard values used by the authors; a water consumption value of 2 liters and a body weight of 70 kg.

[b] The standard error of the mean (SEM) was calculated for the lower bound, assuming a normal distribution of the ED01.

[c] The values provided are the median and in parentheses are the 5^{th} and 95^{th} percentiles of the uncertainty distribution (CI90%).

The width of the confidence intervals for the models derived from Morales *et al.* (2000) is much narrower than that in the FDA models (2013 and current). This is largely attributable to the representation of additional sources of uncertainty in the latter. In particular, the FDA models reflect uncertainty in the dose estimates and the individual dose-response models used to estimate the disease frequency at low doses, while the Morales *et al.* (2000) does not.

3.2.2 LIAO *ET AL.* (2009) MODEL

Liao *et al.* (2009) modeled ecological data from both northeastern and southwestern Taiwan, using a Weibull model. However, because the power parameter for the model was unrestricted, the estimated dose-response relationships were largely supralinear, resulting in biologically implausible incremental risk estimates that increased as the dose decreased.

3.3 COMPARISON OF DOSE-RESPONSE MODELS

The dose-response models based on a prospective epidemiology study in northeastern Taiwan (Chen *et al.*, 2010a,b) and the dose-response model used in the U.S. EPA 2001 drinking-water rule (Morales *et al.*, 2000, model 1 for both sexes combined) are presented for bladder and lung cancer in Figures 3.2 and 3.3, respectively. Comparisons of risk estimates at lower levels, including levels that normally occur from dietary exposure in the United States, are given in Tables 3.5 and 3.6.

The risk estimates from the current FDA model for lung cancer are comparable to those in theapple juice risk assessment (Carrington *et al.*, 2013), but the bladder cancer estimates are lower. This is largely attributable to two factors. First, the estimated average arsenic concentration for the highest dose increased by a factor of almost two (see Section 3.1.3 for discussion of improvements made to the dose-response model). Second, the low-dose uncertainty characterization places a little more on nonlinear models than in the previous assessment. Although the dose estimate at the high dose for lung cancer was also increased, the overall dose-response relationship became more linear than in the previous version, which resulted in low-dose risk estimates that are about the same.

Overall, the estimates from the current FDA model and the 2001 EPA model are quite similar. The two main differences are that (1) the Morales *et al.* (2000) model used to support the 2001 EPA drinking-water rule is entirely linear, and the current FDA model is not, and (2) the confidence interval of Morales *et al.* (2000) is much narrower. The latter difference is attributable to the inclusion, in the current FDA model, of uncertainties arising from the dose estimates and the choice of model used to estimate effects that may arise from dietary exposure. The confidence intervals of the Morales *et al.* (2000) models are entirely encompassed by those of the FDA models for both endpoints.

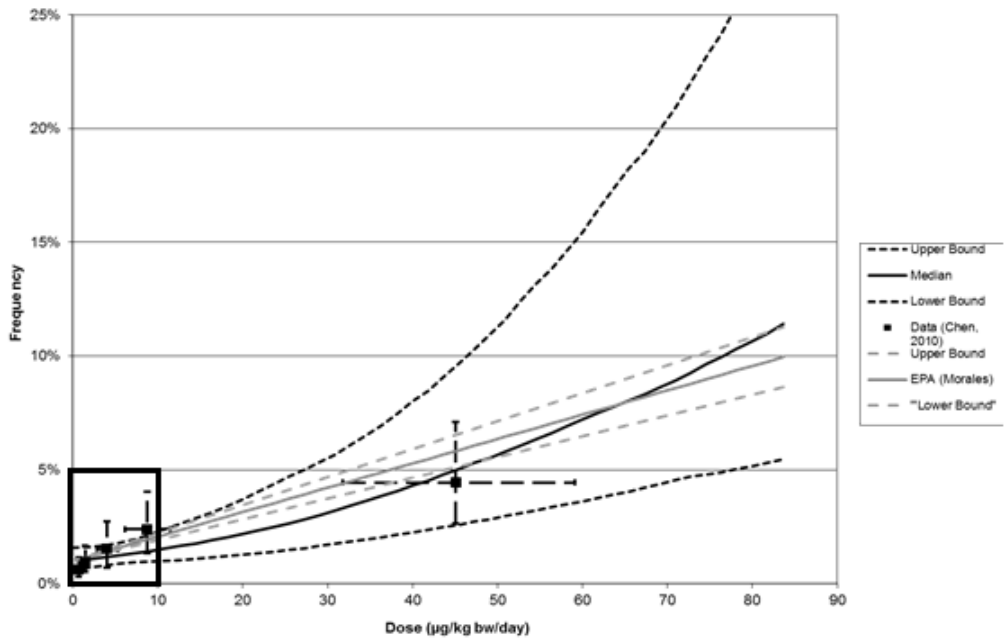

Figure 3.2a. Dose-Response Models for Bladder Cancer
Dose-response model for bladder cancer, based on a prospective epidemiology study in northeastern Taiwan (Chen *et al.*, 2010a). The confidence intervals (5^{th} and 95^{th} percentiles) reflect uncertainties arising from the dose estimates and the frequency estimates (represented by the error bars) and the model used to represent the dose-response relationship. For comparison, the estimates from the model used in the U.S. EPA 2001 drinking-water rule (model 1 from Morales *et al.*, 2000) are shown in gray. See enlarged area of the figure below (Figure 3.2b).

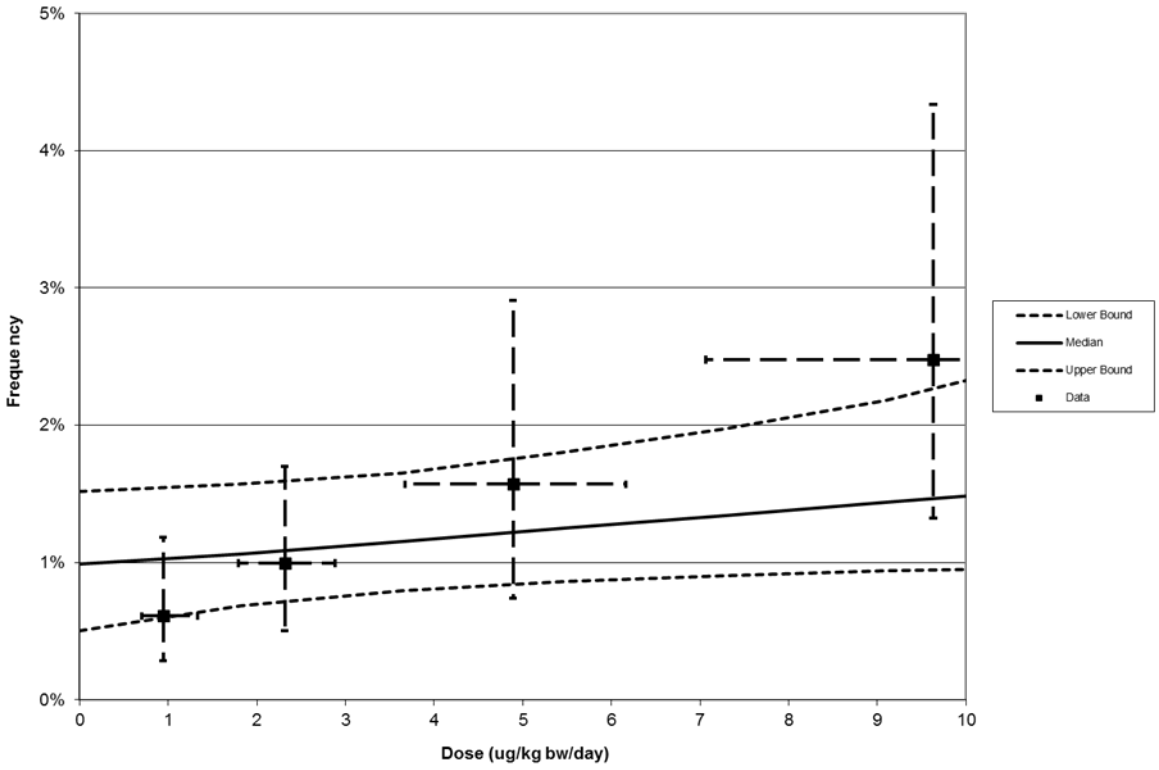

Figure 3.2b. Dose-Response Model for Bladder Cancer, Dose 0 – 10 µg/kg bw/day

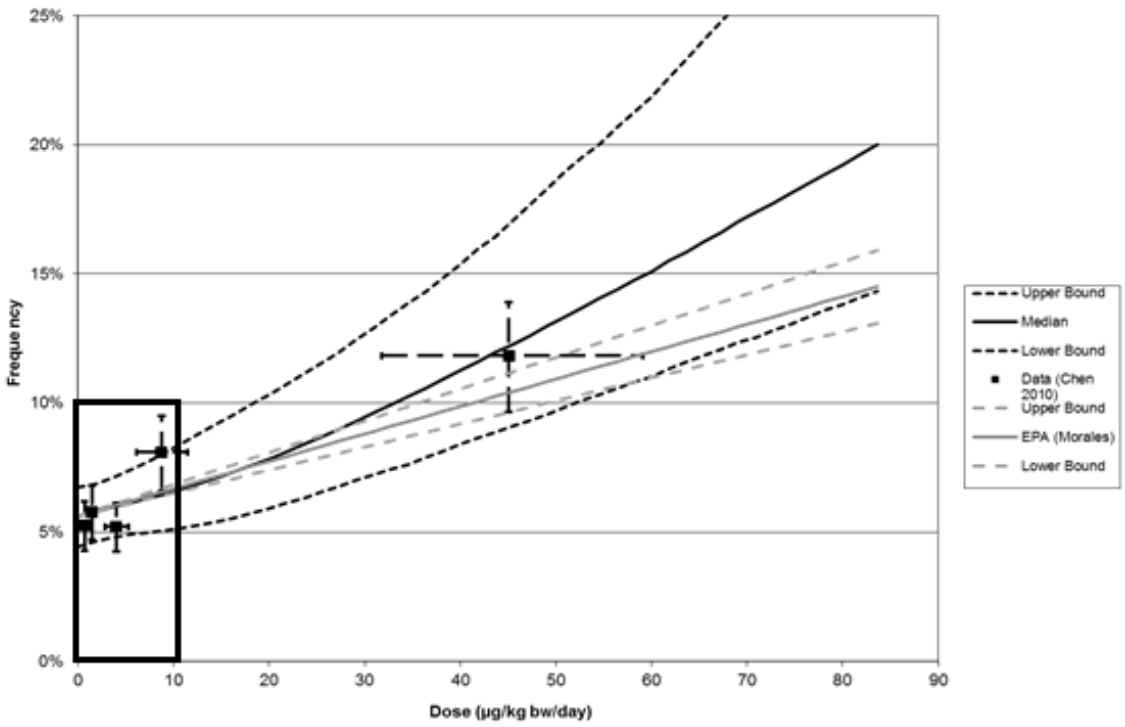

Figure 3.3a. Dose-Response Models for Lung Cancer

Dose-response model for lung cancer, based on a prospective epidemiology study in northeastern Taiwan (Chen *et al.*, 2010b). The confidence intervals (5^{th} and 95^{th} percentiles) reflect uncertainties arising from the dose estimates and the frequency estimates (represented by the error bars) and the model used to represent the dose-response relationship. For comparison, the estimates from the model used in the U.S. EPA 2001 drinking-water rule (model 1 from Morales *et al.*, 2000) are shown in gray. See enlarged area of the figure below (Figure 3.3b).

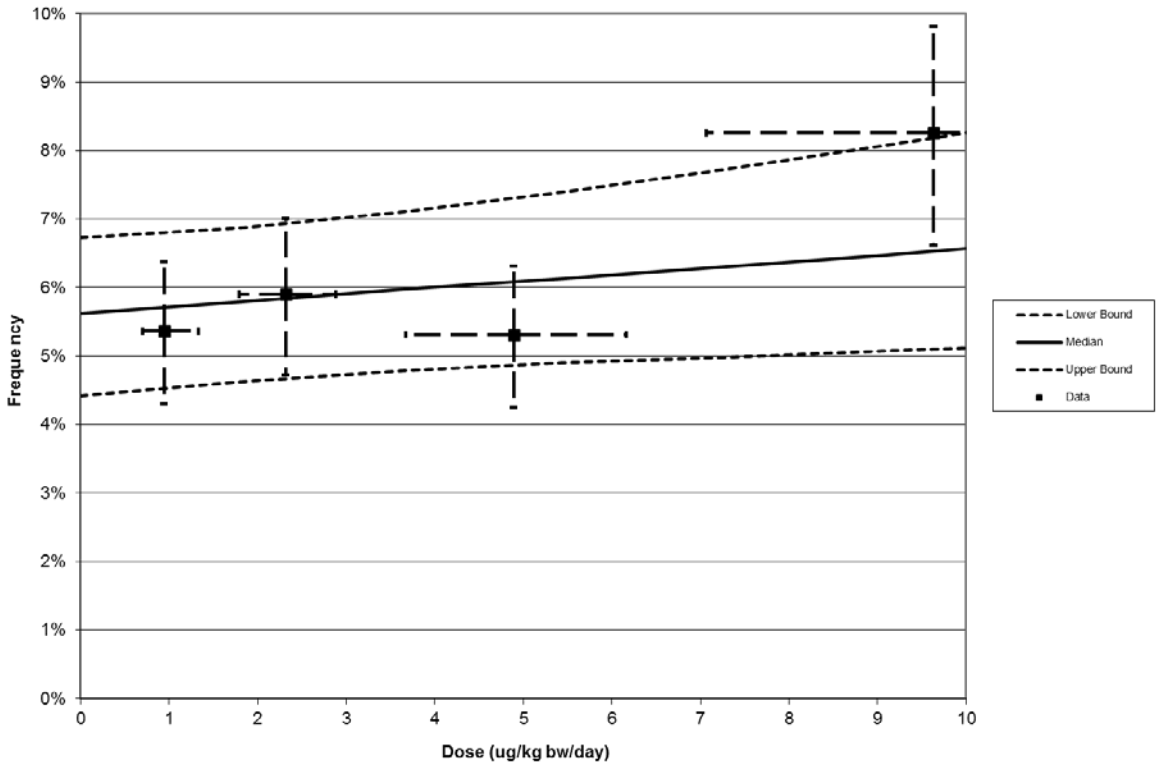

Figure 3.3b. Dose-Response Model for Lung Cancer, Dose 0 – 10 µg/kg bw/day

Table 3.5. Predicted Cases per Million for Bladder Cancer at Five Doses with Lifetime Exposure

Model[a]	Dose[b] 0.029[c] (µg/kg bw/day)	Dose 0.3[d] (µg/kg bw/day)	Dose 1 (µg/kg bw/day)	Dose 3[e] (µg/kg bw/day)	Dose 10 (µg/kg bw/day)
EPA (2001)	31 (26, 35)	325 (277, 372)	1082 (923, 1241)	3246 (2768, 3724)	10819 (9226, 12412)
Carrington *et al.* (2013)[f]	32 (0, 69)	338 (0, 726)	1143 (1, 2483)	3574 (43, 7441)	12968 (2256, 25100)
FDA (current)[g]	11 (0, 43)	114 (0, 458)	383 (0, 1525)	1186 (1, 4568)	4461 (151, 15144)

[a] All estimates are change in frequency of disease over background rate and were calculated using an exposure period of 50 years.

[b] The values provided are the median and in parentheses are the 5th and 95th percentiles of the uncertainty distribution (CI90%).

[c] Dose from tap water at 2 µg/L, 1L/day, 70 kg bw.

[d] Corresponds to current EPA Reference Dose for non-cancer effects (EPA, 2003).

[e] Corresponds to 2011 JECFA $BMDL_{0.5}$.

[f] Estimate from the model version used in FDA's apple juice risk assessment (Carrington *et al.*, 2013).

[g] Estimate from the model version used in this risk assessment for rice and rice products.

Table 3.6. Predicted Cases per Million for Lung Cancer at Five Doses with Lifetime Exposure

Model[a]	Dose[b] 0.029[c] (µg/kg bw/day)	Dose 0.3[d] (µg/kg bw/day)	Dose 1 (µg/kg bw/day)	Dose 3[e] (µg/kg bw/day)	Dose 10 (µg/kg bw/day)
EPA (2001)	32 (27, 37)	338 (284, 391)	1125 (947, 1304)	3376 (2840, 3912)	11254 (9467, 13041)
Carrington *et al.* (2013)[f]	30 (0, 123)	369 (0, 1292)	1284 (0, 4298)	4634 (7, 13594)	20242 (1763, 43882)
FDA (current)[g]	32 (0, 62)	336 (0, 654)	1123 (0, 2178)	3399 (4, 6517)	11674 (585, 21549)

[a] All estimates are change in frequency of disease over background rate and were calculated using an exposure period of 50 years.

[b] The values provided are the median and in parentheses are the 5th and 95th percentiles of the uncertainty distribution (CI90%).

[c] Dose from tap water at 2 µg/L, 1L/day, 70 kg bw.

[d] Corresponds to current EPA Reference Dose for non-cancer effects (EPA, 2003).

[e] Corresponds to 2011 JECFA $BMDL_{0.5}$.

[f] Estimate from the model version used in FDA's apple juice risk assessment (Carrington *et al.*, 2013).

[g] Estimate from the model version used in this risk assessment for rice and rice products.

4 EXPOSURE ASSESSMENT

Dietary exposure to inorganic arsenic is a function of the levels of inorganic arsenic concentrations in food and the quantity of inorganic arsenic-containing food consumed. This section presents the inorganic arsenic concentration and rice consumption data used to assess dietary exposure to inorganic arsenic. The exposure assessment provided in this section (with additional details in appendices 9.8 – 9.12) is used for both cancer and non-cancer risk characterization (see Sections 5 and 6)

4.1 THE EXPOSURE ASSESSMENT MODEL (COMPONENTS)

Figure 4.1 provides an overview of the Exposure Assessment components of the Monte-Carlo simulation model that integrated the concentration of inorganic arsenic in food, food consumption, market share, and bioavailability data, to estimate inorganic arsenic intake from rice and rice products. Details on the data used for the Exposure Assessment components of the simulation model are provided in this section.

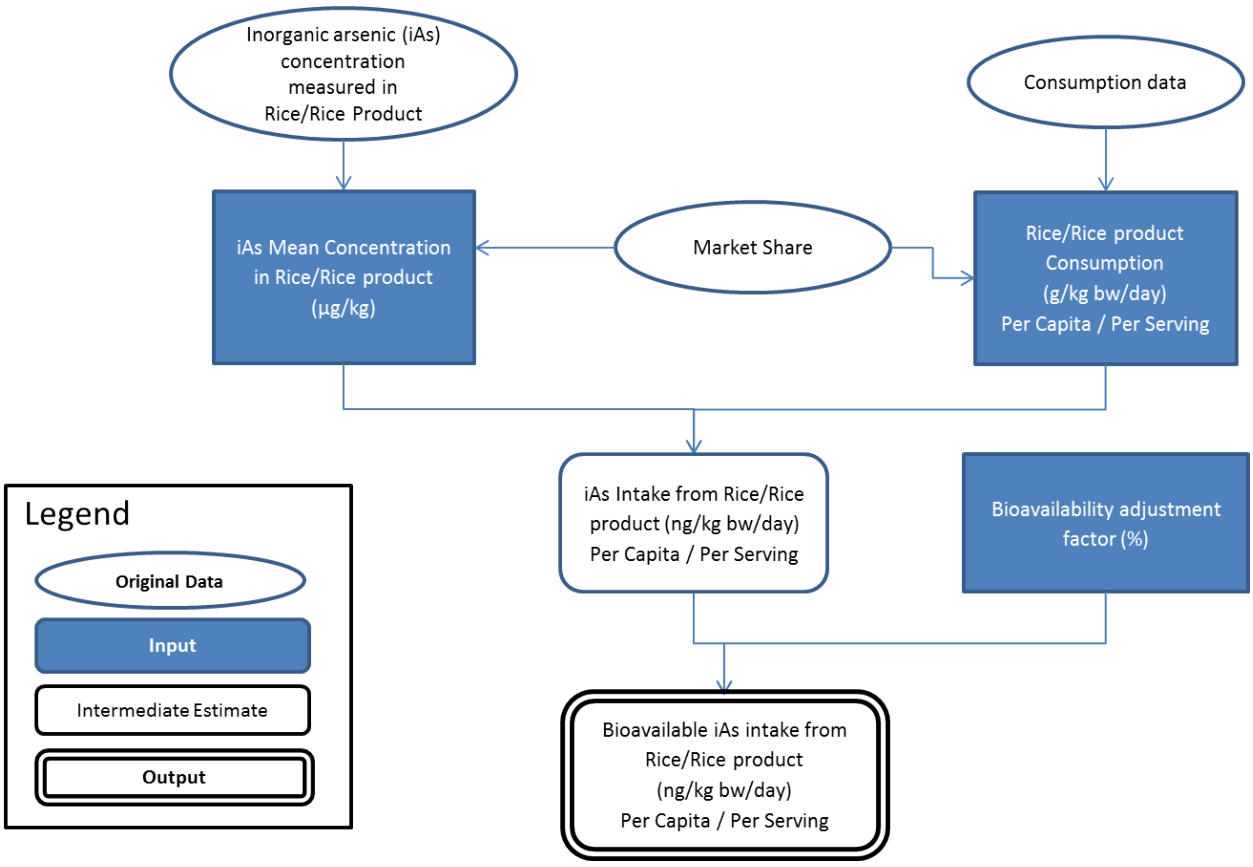

Figure 4.1. Model Used to Estimate Inorganic Arsenic Intake from Rice and Rice Products

4.2 INORGANIC ARSENIC CONCENTRATION DATA

This risk assessment utilized data on concentrations of inorganic arsenic in rice grain to estimate exposure to rice consumed alone and as an ingredient in food mixtures (e.g., casseroles, crackers, rice beverages). Separate analyses were conducted for exposure during infancy, using data on concentrations of inorganic arsenic in infant rice cereal to estimate inorganic arsenic intakes by infants less than 1 year of age.

4.2.1 DATA IDENTIFICATION AND SELECTION

Data on inorganic arsenic levels in U.S. rice grain and infant cereals are available from two sources: (1) FDA surveys (FDA, 2013; FDA, 2016) and (2) data reported in the literature. To identify published sources of total arsenic and inorganic arsenic concentration data, we contracted with the Oak Ridge National Laboratory to conduct a systematic literature review, to identify studies reporting results of analyses of inorganic arsenic concentrations in market samples of rice. The following terms were used to identify potential data sources on arsenic concentration and exposure: arsenic AND rice AND (composition OR concentration OR content OR intake OR exposure OR ingestion OR consumption), 1993 to the present. Databases searched included Pubmed, Toxline, and Web of Science. A total of 299 studies were identified in the Pubmed search, and 66 additional studies were identified in the Toxline search. The initial Web of Science search listed thousands of publications; after eliminating citations for studies relating to site remediation, the search resulted in citations for 206 studies. Publications judged to be potentially relevant, based on abstract contents, were obtained and further reviewed for relevance. Using these criteria, 14 studies were identified for further review. The most comprehensive of the 14 studies was conducted by Consumer Reports (2012). Of the remaining 13 studies, 4 were found to contain data appropriate for comparison with FDA data; the excluded studies measured arsenic concentrations on samples purchased or originating outside the United States, did not provide adequate sample descriptions, or did not measure inorganic arsenic in the collected samples. Criteria applied to selection of data for inclusion in the exposure assessment are shown in Table 4.1. Only one published study (Consumer Reports, 2012) in addition to the FDA (2013, 2016) surveys met the selection criteria listed in Table 4.1 for inclusion in the risk-assessment model.

Table 4.1. Selection of Data Used for the Exposure Assessment Model

Study	Number of samples >100	Wide variety of rice types and infant cereals	Published within previous 5 years	Nationally representative	Included in risk assessment?
FDA surveys	Yes (481 grain; 145 infant cereals – total 1419 samples)	Yes	Yes	Yes	Yes
Consumer reports, 2012	Yes (92 grain; 12 infant cereals – total 223 samples)	Yes	Yes	Yes (New York metro area and online retailers)	Yes
Zavala *et al.* 2008	No (24)	Yes	No	Yes	No
Williams *et al.* 2005	No (11)	No (white and brown rice grain)	No	No	No
Lamont, 2003	No (40)	No (white rice grain)	No	Yes	No
Schoof *et al.* 1999	No (4)	No (white rice grain)	No	No	No

Note: Literature search included studies published up to October 2013.

4.2.2 2013 AND 2016 FDA ARSENIC IN RICE SURVEYS

In 2013 FDA reported concentrations of arsenic and arsenic species (arsenite, arsenate, DMA, and MMA) in 1,343 samples, including 481 samples of rice grain and 69 samples of infant cereals (FDA, 2013). FDA analyzed 76 additional infant cereal samples in 2014 (FDA, 2016). . The FDA 2013 study generated arsenic concentration data for 786 samples of processed rice products and 6 samples of wild rice and grain mixtures. The data on inorganic arsenic concentrations in processed rice products were not used in the present risk assessment because data were not available for all processed rice products consumed by Americans. The data on inorganic arsenic concentrations in rice grain and infant cereals were used in this risk assessment to estimate exposure to inorganic arsenic from all rice sources. A summary of these study results is provided in Appendix 9.5.

Of the 481 samples of rice grain, 202 retail samples were collected by FDA at retail locations and 279 samples were supplied by the USA Rice Federation.

Total arsenic concentrations in market rice samples were determined using inductively coupled plasma-mass spectrometry (ICP-MS) after acid hydrolysis. Speciated arsenic concentrations were measured using high performance liquid chromatography-inductively coupled plasma-mass spectrometry (HPLC-ICP-MS) (Kubachka *et al.*, 2012).

Mean inorganic arsenic concentrations in types of rice grain and in dry infant rice cereal are shown in Table 4.2. For types of rice with more than one analyzed sample, mean inorganic arsenic concentrations ranged from 58 ppb in white, instant/pre-cooked rice to 160 ppb in regular brown rice. Relatively high inorganic arsenic concentrations in parboiled rice may result from boiling the rice in the husk before drying and polishing; parboiling is thought to modify the rice starch, permitting greater retention of vitamins and minerals in the kernels (Jorhem *et al.*, 2008). The mean inorganic arsenic concentration in dry infant brown-rice cereal was 120 ppb, and the mean inorganic arsenic concentration in dry infant white-rice cereal was 105 ppb.

Table 4.2. Concentration of Inorganic Arsenic in Rice Grain and Infant Rice Cereal Samples Analyzed by FDA

Rice Type (uncooked/unprepared)	n	Inorganic Arsenic Mean Concentration[a,b] (ppb[c])	Inorganic Arsenic SEM[d] (ppb)	Range of Inorganic Arsenic Concentration (ppb)
Brown Basmati; includes pre-cooked	13	122.7	11.3	66 – 200
Brown Jasmine	2	132.5	18.5	114 – 151
Brown Instant/pre-cooked, other than basmati	2	72.0	7.1	65 – 79
Brown Parboiled	1	191.3	N/A[e]	N/A
Brown Long/medium/short grain, regular	98	160.5	4.1	34 – 249
White Basmati; includes pre-cooked	40	61.8	3.9	20 – 144
White Jasmine	11	78.4	6.6	34 – 110
White Instant/pre-cooked, other than basmati	14	57.6	7.5	31 – 134
White Parboiled	38	111.9	3.8	71 – 182
White Long grain, regular	148	103.3	2.2	23 – 196

Rice Type (uncooked/unprepared)	n	Inorganic Arsenic Mean Concentration[a,b] (ppb[c])	Inorganic Arsenic SEM[d] (ppb)	Range of Inorganic Arsenic Concentration (ppb)
White Medium grain, regular	91	80.9	2.6	39 – 174
White Short grain, regular	23	78.9	3.5	52 – 102
Infant Brown Rice Cereal	59	119.9	6.4	30 – 254
Infant White Rice Cereal	86	105.3	2.2	21 – 151

[a] Data source: FDA (2013) and FDA (2016).

[b] Arithmetic mean. For one brown and one white basmati rice sample, inorganic arsenic concentration was imputed as half of the total As.

[c] ppb = µg/kg or ng/g

[d] SEM = standard error of the mean.

[e] N/A = not applicable.

4.2.3 CONSUMER REPORTS SURVEY

The 2012 Consumer Reports study measured arsenic and arsenic-species concentrations in 92 samples of packaged, uncooked rice; 12 samples of infant rice cereals; and samples of other rice-containing foods purchased from retail sources in the U.S. In general, Consumer Reports analyzed three samples of each rice type and brand. Samples from this study were analyzed for total arsenic concentrations, using Inductively Coupled Plasma-Dynamic Reaction Cell-Mass Spectrometry (ICP-DRC-MS) and for inorganic arsenic species concentrations using Ion Chromatography- ICP-DRC-MS, both of which produce results comparable to the methods used by FDA. Consumer Reports' inorganic arsenic concentrations for most rice grain samples were within the ranges found by FDA (2013), although one U.S.-grown brown basmati sample and one U.S.-grown brown jasmine sample exceeded the upper range of values FDA found in those two products.

4.2.4 INORGANIC ARSENIC CONCENTRATION DATA USED IN THE FDA EXPOSURE ASSESSMENT

Data from the FDA (2013, 2016) and Consumer Reports (2012) studies were combined for this assessment. Data for individual FDA and Consumer Reports samples were categorized by type of rice, as noted in Table 4.3. For each type of rice grain, the mean level of inorganic arsenic and its standard error were estimated from the measured-concentration data.

Table 4.3. Concentration of Inorganic Arsenic in Rice Grain and Infant Rice Cereal Samples: Combined FDA (2013, 2016) and Consumer Reports (2012) Data

Rice Type (uncooked/unprepared)	n	Inorganic Arsenic Mean Concentration[a,b] (ppb[c])	Inorganic Arsenic SEM[d] (ppb)	Range of Inorganic Arsenic Concentration (ppb)
Brown Basmati; includes pre-cooked	16	133.3	11.5	66 – 210
Brown Jasmine	5	142.4	15.5	104 – 191
Brown Instant/pre-cooked, other than basmati	2	72.0	7.1	65 – 79
Brown Parboiled[e]	1	191.3	N/A	N/A
Brown Long/medium/short grain, regular	120	156.5	3.7	34 – 249
White Basmati; includes pre-cooked	58	62.3	3.2	20 – 144
White Jasmine	23	75.1	3.5	34 – 110
White Instant/pre-cooked, other than basmati	14	57.6	7.5	31 – 134
White Parboiled	44	112.4	3.5	71 – 182
White Long grain, regular	173	102.0	2.0	23 – 196
White Medium grain, regular	94	81.5	2.5	39 – 174
White Short grain, regular	23	78.9	3.5	52 – 102
Infant Brown Rice Cereal	65	119.0	6.1	30 – 254
Infant White Rice Cereal	92	103.9	2.2	21 – 151

[a] Data source: FDA (2013), FDA (2016) and Consumer Reports (2012).

[b] Arithmetic mean. For one brown and one white basmati rice sample, inorganic arsenic (iAs) concentration was imputed as half of the total As.

[c] ppb = µg/kg or ng/g

[d] SEM = standard error of the mean.

[e] N/A = not applicable; a SEM value of 50 ppb was used for brown parboiled for calculation purposes

4.2.5 MARKET SHARE

We used market-share data for two purposes (as indicated in Figure 4.1). The 2013 and 2016 FDA rice-sampling studies and the Consumer Reports (2012) publication provided inorganic arsenic concentrations on specific types of rice. However, we (FDA) wanted to calculate a

weighted mean inorganic arsenic concentration for all brown rice, all white rice, and all rice, so that we could generate estimates of risk related to consumption of these general types of rice. The relative market-share estimates of different types of rice were determined using data from the USDA Economic Research Service (ERS) and USA Rice Federation (Table 4.4; Appendix 9.7). The market shares for basmati, jasmine, instant, and parboiled rice in Appendix 9.7 include both brown and white rice; we used ERS data to divide the market shares for these types of rice into separate market shares for brown and white basmati, jasmine, instant, and parboiled rice. We recalculated the market shares of specific rice types excluding the market share proportion of "other" rice and used the adjusted market share proportions in our analyses.

The resulting weighted mean inorganic arsenic concentrations for all brown rice, all white rice, and all rice are shown in Table 4.5. Because the combined adjusted market share for types of brown rice is only 6%, the weighted mean for inorganic arsenic in all rice (96 ppb) is much closer to the weighted mean for inorganic arsenic in white rice (92.3 ppb) than to the weighted mean for inorganic arsenic in brown rice (153.8 ppb). The detailed calculations are shown in Appendix 9.8.1.

Our second use of market-share data on rice was in estimating rice consumption. Because the available data on rice consumption allow estimation of intakes of white rice and brown rice, but not specific subtypes of rice, we estimated intakes of specific subtypes of rice from all sources (including intakes from rice products), based on estimated market shares for these products.

Table 4.4. Market-Share Percentages for Types of Brown and White Rice

Rice Type	Market share (%)	Adjusted Market share (%)
Brown Basmati	0.9	1.1
Brown Jasmine	0.1	0.1
Brown Instant/pre-cooked	0.2	0.2
Brown Parboiled	0.7	0.8
Brown Long/med/short grain, regular	3.2	3.8
White Basmati	1.8	2.1
White Jasmine	9.1	10.8
White Instant/pre-cooked	2.1	2.5
White Parboiled	8.0	9.5
White Long grain, regular	37.1	44.0
White Medium grain, regular	18.5	21.9
White Short grain, regular	2.6	3.1

Rice Type	Market share (%)	Adjusted Market share (%)
Brewer's/Broken and Other	15.7	—

Note: Determined based on data from the USDA Economic Research Service (ERS) and USA Rice Federation (Appendix 9.7; additional personal communications, Nathan Childs, USDA-ERS).

Table 4.5. Estimated Inorganic Arsenic Concentrations in All Brown Rice, All White Rice, and All Rice Combined

Rice Type (uncooked/ unprepared)	Number of Inorganic Arsenic Data Samples	Inorganic Arsenic Concentration Weighted Mean[a] (ppb)	Inorganic Arsenic Concentration Weighted SEM (ppb)
All	573	96.0	1.2
Brown	144	153.8	3.2
White	429	92.3	1.3

[a] Determined based on inorganic arsenic data on individual rice types from FDA (2013) and Consumer Reports (2012); weighted based on market share from the USDA Economic Research Service (ERS) and USA Rice Federation (Appendix 9.7; additional personal communications, Nathan Childs, ERS).

[b] ppb = µg/kg or ng/g

4.2.6 INORGANIC ARSENIC CONTRIBUTION FROM RICE PRODUCTS

We used the inorganic arsenic concentrations for rice grain described in sections 4.2.4 and 4.2.5 and the Food Commodity Intake Database (FCID) developed by U.S. EPA's Office of Pesticide Programs (OPP) (EPA, 2013b) to estimate the inorganic arsenic contributions from rice products reported by participants in What We Eat in America (WWEIA) 2003 – 2004, 2005 – 2006, 2007 – 2008, and 2009 – 2010 (CDC, 2013). WWEIA is described in more detail in section 4.3.1.FCID translates foods reported by WWEIA respondents into "recipes" indicating proportions of U.S. EPA-defined food commodities contained in each food. Rice commodity codes included in FCID are as follows:

- 1500323000 Rice, white
- 1500323001 Rice, white, baby food
- 1500324000 Rice, brown
- 1500324001 Rice, brown, baby food
- 1500325000 Rice, flour

- 1500325001 Rice, flour, baby food

See Appendix 9.9.1 for a list of the rice-containing foods and the proportions of rice ingredients in each food. For example, the FCID "recipe" for "rice crackers" indicates that this food contains 94.9 g white rice per 100 g crackers. The FCID recipe for "rice beverage" indicates that this food contains 14.9 g brown rice per 100 g of beverage. Using the inorganic arsenic concentration calculated for all white rice in section 4.2.5 (92.3 ppb), the estimated-inorganic arsenic concentration of rice crackers would be 94.9 g white rice/100 g rice crackers multiplied by 92.3 ng iAs/g white rice = 88.2 ng iAs/g rice crackers (88.2 ppb iAs). Using the inorganic arsenic concentration calculated for all brown rice in section 4.2.5 (153.8 ppb), the estimated inorganic arsenic concentration of rice beverage would be 14.9 g brown rice/100 g rice beverage multiplied by 153.8 ng iAs/g brown rice = 22.9 ng iAs/g rice beverage (22.9 ppb iAs).

4.3 INTAKE OF RICE AND RICE PRODUCTS

4.3.1 CONSUMPTION DATA

We estimated intakes of rice from rice grain and rice products using food-consumption data reported in What We Eat in America (WWEIA) 2003 – 2004, 2005 – 2006, 2007 – 2008, and 2009 – 2010 (CDC, 2013) and the FCID database described in Section 4.2.6. WWEIA is the dietary interview portion of the National Health and Nutrition Examination Survey (NHANES). NHANES/WWEIA is a cross-sectional survey designed to provide nationally representative prevalence estimates for nutrition and health status measures in the United States. WWEIA participants provide 24-hour recalls of all foods and beverages consumed over each of 2 non-consecutive days. Estimates of rice intake used in the risk assessment were generated using the latest NHANES/WWEIA survey cycle (2009 – 2010); we also estimated intake using data from the combined years 2003–2010 to assess rice intakes based on a larger sample size and to identify any major recent shifts in rice consumption. Mean rice and inorganic arsenic intakes were estimated using NHANES statistical weights developed for the two-day dietary data, to correct for differences in population response rates.

Rice consumption was estimated using two different measures: 1) per capita daily intake of uncooked rice from all sources (rice grain and rice products) and 2) consumption of uncooked rice grain per eating occasion. In the absence of longitudinal data on rice consumption by individuals over the course of their lifetimes, it was assumed that average lifetime intakes of rice and rice products can be approximated by estimates of mean per capita rice intakes (average daily intakes for the entire population, including consumers and non-consumers) by participants in the cross-sectional NHANES/WWEIA. We estimated mean intakes by consumers of rice per eating occasion to allow estimation of risk by individuals who consume rice grain on one

occasion or multiple occasions per day over a lifetime. (See "What If" scenarios provided in Sections 5 and 6.) Throughout this risk assessment, the terms "serving" and "serving size" are used to describe the average amount of rice consumed when rice grain is consumed alone; this "serving size" is not the same as the serving size that appears on rice labels. The body weight of each NHANES respondent was used to convert rice intakes in g/day or g/eating occasion to intake in g/kg bw/day or g/kg bw/eating occasion.

NHANES/WWEIA-based rice intake analyses were conducted using Food Analysis and Residue Evaluation Program (FARE) v. 10.05 (Durango Software LLC). Mean per capita two-day average intakes of brown rice, white rice (including rice flour), and all rice were estimated to characterize intakes at less than 1 year of age, during 0 – 6 years (inclusive) of age, and 0 – 50 years of age (inclusive).

The information on types of rice consumed by NHANES/WWEIA respondents was generally limited to the level of processing (i.e., brown or white); no information was collected or recorded on grain size or variety (e.g., basmati or jasmine). Therefore, the intakes of specific categories of rice (those for which inorganic arsenic were analyzed) were estimated by multiplying the total intake amounts of white and of brown rice generated using FARE by the market-share data shown in Table 4.4. Detailed calculations are shown in Appendix 9.8.2.

For the estimates of rice intake per eating occasion, an eating occasion was defined as a single instance of consumption of rice as a single food (not as an ingredient in NHANES/WWEIA codes for food mixtures), regardless of whether the rice was consumed at a meal or as a snack. Intakes of rice from infant rice cereal were estimated, per eating occasion, for infants less than 1 year old. Intakes of plain brown rice, white rice, and combined brown and white rice were estimated, per eating occasion, for individuals 0 – 6 years old and 0 – 50 years old. See Appendix 9.8.2 for a list of the food codes used in these analyses.

To assess the proportion of individuals who consume rice on one or more occasions per day, we estimated the frequency of rice consumption by NHANES/WWEIA participants. These rice frequency estimates were not used in the risk assessment model; we conducted these analyses to understand how frequency of rice consumption varies among ethnic groups and to inform the "What-If" Scenarios described in Sections 5 and 6.

The frequency of rice consumption was estimated using food-frequency data reported by participants for those ages 2 years and older in the 2003 – 2004 and 2005 – 2006 NHANES/WWEIA (detailed food-frequency data were not collected in later NHANES surveys). Responses to the question "How often did you eat rice or other cooked grains (such as bulgur, cracked wheat, or millet)?" were analyzed to compute mean rice-eating occasions per day, using the factors presented in Appendix 9.10.

We assumed that rice was the grain consumed in most or all grain-frequency responses. The relative frequency of rice/other grain consumption was analyzed for the total population ages 2 years and older and by ethnicity (Mexican-American, Other Hispanic, White Non-Hispanic, Black Non-Hispanic, and "other," including Asian and multi-racial), as defined in the NHANES/WWEIA surveys.

4.3.2 RESULTS: ESTIMATES OF PER CAPITA RICE INTAKES

Mean per capita estimates of rice intake (g/kg bw) used in the risk assessment are summarized in Table 4.6. Additional data generated for reference (including data on rice intakes in g/day and g/eating occasion) are shown in Tables 9.25 – 9.29 in Appendix 9.11.

Table 4.6. Rice-Intake Data Used in the Risk Assessment

Population Group	NHANES/WWEIA Survey Year[a]	Rice Products	Mean Uncooked Rice Per Capita Daily Intake[b] (g/kg bw)	Mean Uncooked Rice Intake Per Eating Occasion (g/kg bw)
< 1 year	2003 – 2010	Infant rice cereal	0.664	1.125
< 1 year	2003 – 2010	All rice grain and products	0.925	N/A[c]
0 – 6 years	2009 – 2010	All rice grain and products	0.566	N/A[c]
0 – 6 years	2009 – 2010	Brown-rice grain and products	0.046	1.01
0 – 6 years	2009 – 2010	White-rice grain and products	0.520	1.929
0 – 50 years[d]	2009 – 2010	All rice grain and products	0.332	N/A[c]
0 – 50 years[d]	2009 – 2010	Brown-rice grain and products	0.029	0.866
0 – 50 years[d]	2009 – 2010	White-rice grain and products	0.303	1.094

[a] Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), years as noted in the table. Food codes included in analysis are listed in Appendices 9.9.1 and 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert his/her intake in g/day to intake in g/kg bw/day.

[b] Per capita means are calculated as the average intakes by consumers and non-consumers.

[c] N/A = not applicable. See section 4.3.3.

[d] Because of the apparent 25-30 year latency between exposure and effect, the relevant period of exposure for the carcinogenics effects for arsenic is estimated to be 0 – 50 years of age.

While we considered it preferable to use 2009 – 2010 NHANES/WWEIA consumption data in the risk assessment, to reflect current consumption practices, intakes of rice from infant rice cereal were higher in the combined 2003 – 2010 surveys; therefore, the combined survey data were used in the risk assessment as a conservative estimate of rice-cereal intake by infants. On average, infant respondents in the 2003 – 2010 NHANES/WWEIA consumed about 5 g dry infant rice cereal, or 0.664 g rice cereal/kg bw per day; 5 g is equivalent to about 2 tablespoons (T) of dry infant rice cereal. Mean per capita intake of rice from all sources (infant rice cereal and regular rice) was 7.4 g, or 0.925 g/kg bw/day; 7.4 g is equivalent to about 3 T of dry infant cereal. The amount of rice cereal consumed per day over the first year of life (g/kg bw/day) peaks between 5 and 9 months of age (Figure 4.2). The number of infants included in the NHANES/WWEIA sample at each month of age ranged from 119 to 145. The number of infant-cereal consumers ranged from 10 during the first month of life to 81 at 5 months of age.

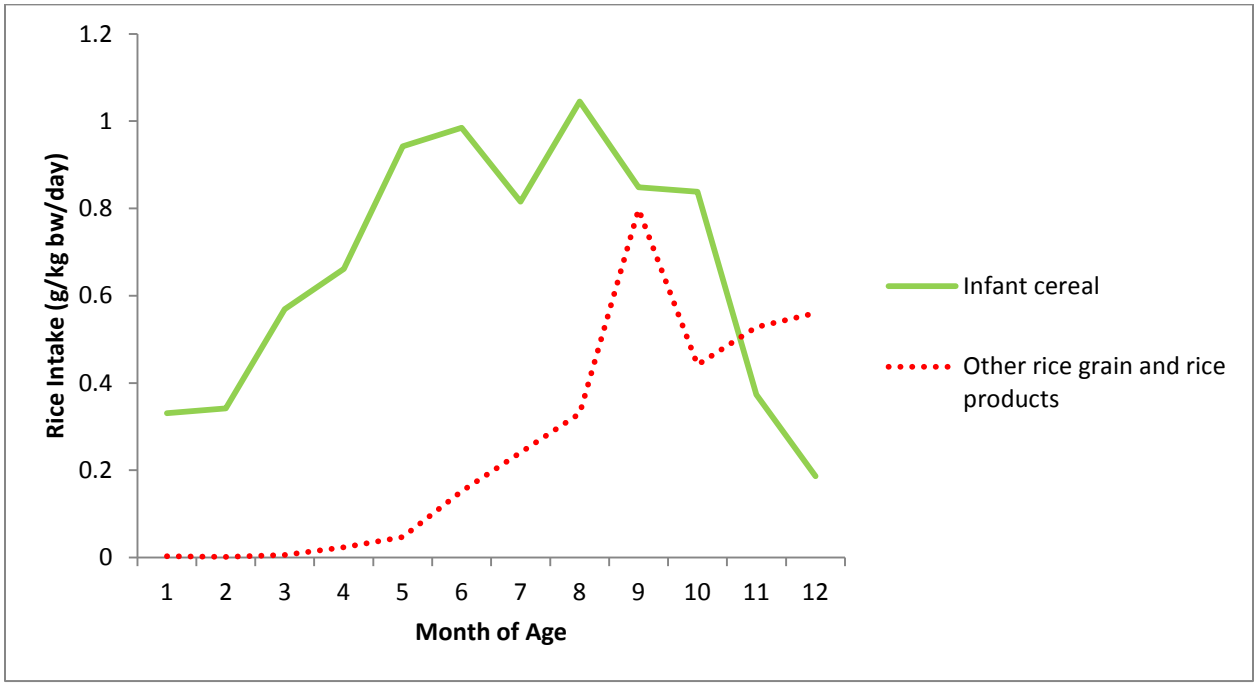

Figure 4.2. Intake of Infant-Rice Cereal and Other Rice Grain and Rice Products by Children 0 – 12 Months of Age

Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.1. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert his/her intake in g/day to intake in g/kg bw/day.
N at each month of age ranged from 119 to 145. The number of infant-cereal consumers ranged from 10 during the first month of life to 81 at 5 months of age.

For the 0 – 6 year and 0 – 50 year exposure groups, rice intakes in 2009 – 2010 were higher or comparable to those in 2003 – 2010. Estimates of mean per capita rice intakes from all sources (rice grain and rice products) during the periods 0 – 6 years and 0 – 50 years are shown in Table 4.6.

Mean per capita intake of rice by males and females 0 – 6 years who participated in the 2009 – 2010 NHANES/WWEIA was 8.4 g, or 0.566 g/kg bw/day. An intake of 8.4 g is equivalent to about 1/5 of a cup of cooked rice. Mean per capita daily intake of rice by males and females 0 – 50 years during the 2009 – 2010 survey was about 19 g, or 0.332 g/kg bw/day; 19 g is equivalent to about 1/3 of a cup of cooked rice. About 11% of rice consumers in both age groups reported consuming brown rice at least once during the 2-day survey. Changes in rice consumption by life stage and gender are shown graphically in Figure 4.3.

The results of an exploratory analysis of rice intake from sources other than beer (Figure 4.4) indicate that most of the difference in rice intake between males and females is due to greater intake of rice from beer by males than by females. We included rice intake from beer in estimating inorganic arsenic exposure from rice for our risk assessment.

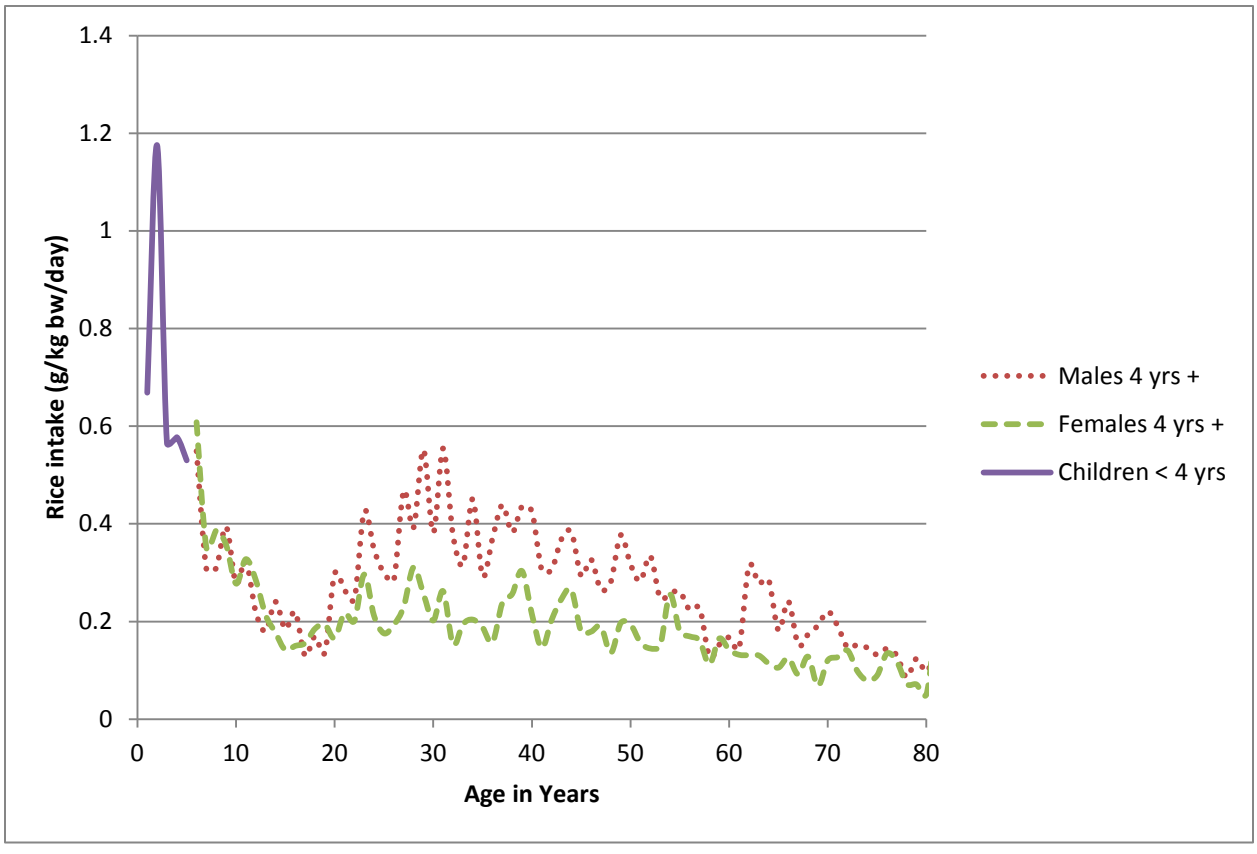

Figure 4.3. Consumption of Rice, Mean per Capita Daily Intake from All Sources (Rice Grain and Rice Products) by Age and Gender

Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.1. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population response rates. The body weight of each NHANES respondent was used to convert his/her intake in g/day to intake in g/kg bw/day.

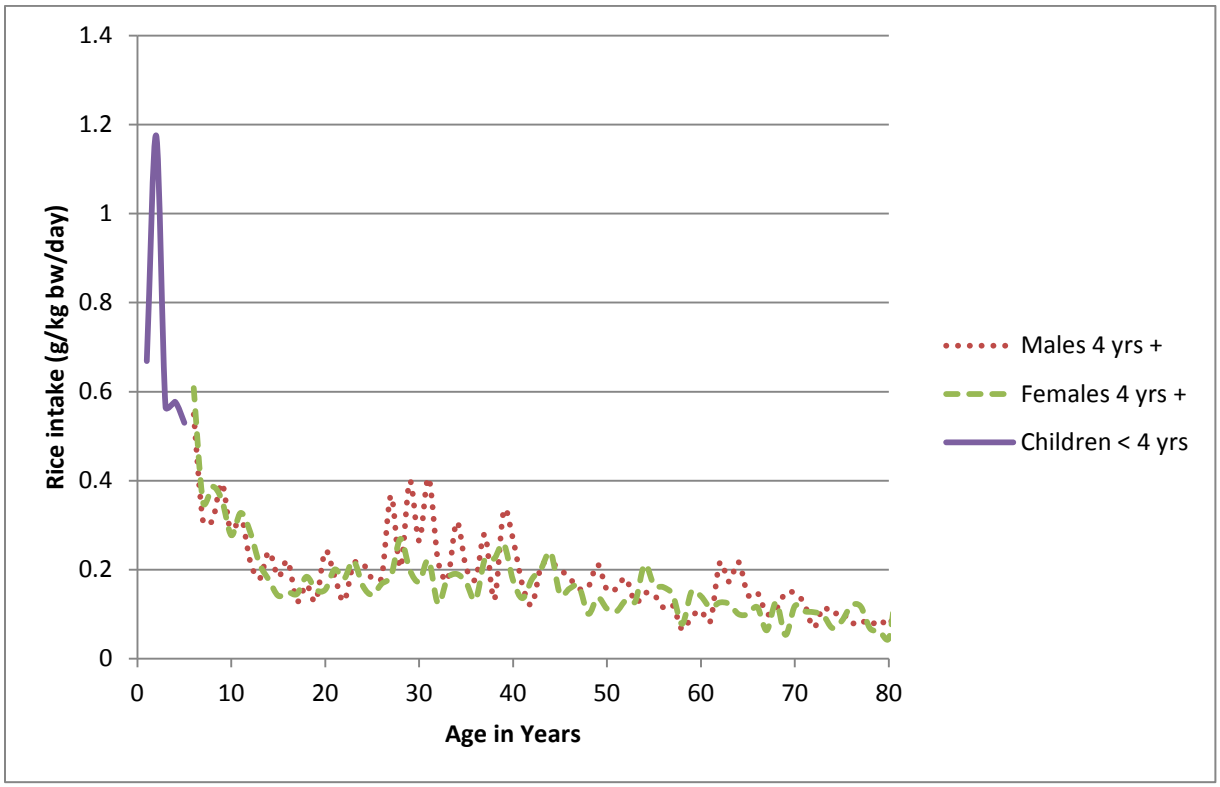

Figure 4.4. Consumption of Rice, Excluding Consumption as an Ingredient in Beer, Mean per Capita Daily Intake by Age and Gender

Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.1. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population response rates. The body weight of each NHANES respondent was used to convert his/her intake in g/day to intake in g/kg bw/day.

4.3.3 RESULTS: ESTIMATES OF PER SERVING (EATING OCCASION) RICE INTAKE

The mean intake of rice from dry infant cereals per eating occasion, by infants less than 1 year of age was 1.125 g/kg bw, based on 2003 – 2010 NHANES/WWEIA data (Table 4.6; additional data are provided in Table 9.5). Eating occasion data were combined for all infant rice cereal (brown and white), because the number of consumption occasions for brown rice was too low to be statistically meaningful.

Intakes of rice per eating occasion by older age groups (based on 2009 – 2010 NHANES/WWEIA data) are shown in Tables 4.6 and 9.6. For the subpopulation ages 0 – 6 years, mean intakes per eating occasion were 1.01 g brown rice/kg bw and 1.929 g white rice/kg bw. For the subpopulation ages 0-50 years, mean intakes per eating occasion were 0.866 g brown rice/kg bw and 1.094 g white rice/kg bw. The mean intake amounts of white rice per eating occasion are 15.7 g for ages 0 – 6 years (equivalent to a little bit more than 1/2 cup of cooked rice) and 32 g for ages 0 – 50 years (a little bit more than 1 cup of cooked rice).

4.3.4 RESULTS: FREQUENCY OF INTAKE

In characterizing usual consumption frequency for rice or other grains, the response category with the greatest proportion of responses (20% of NHANES respondents for those ages 2 years and older) was "2 – 3 times per month" (Figure 4.5). The mean per capita frequency of consumption of rice or other cooked grains was estimated to be 0.2 eating occasions per day (Table 4.7). In the total population, 3.4% of individuals reported consuming rice or other cooked grains at least once a day; however, 32.6% of individuals in the "other" ethnic group, which includes Asians and multi-racial individuals, reported consuming rice or other cooked grains at least once a day. These results indicate that, while it might be appropriate to base estimates of risks from intakes of inorganic arsenic on per capita intakes of rice for the general population, there are groups (e.g. Asians) in which high proportions of individuals consume rice on a daily basis. For those populations, risks from intakes of inorganic arsenic in rice are more appropriately estimated based on the average number of daily rice eating occasions over a lifetime.

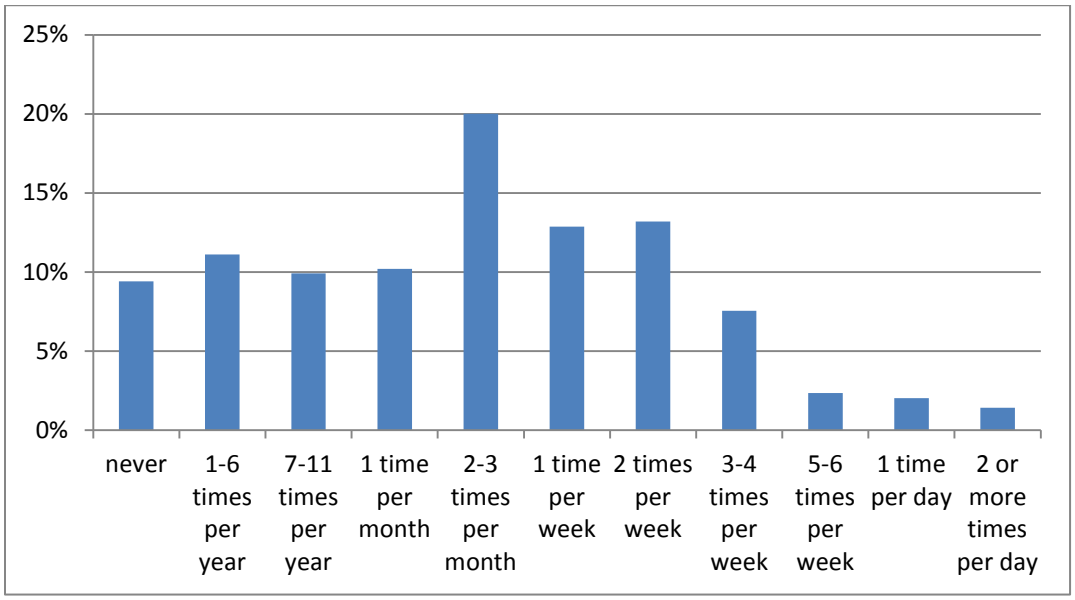

Figure 4.5. Frequency of Consumption of Rice and Other Cooked Grains
Data source: National Health and Nutrition Examination Survey (NHANES), 2003-2004 and 2005-2006, Food Frequency Questionnaire question FFQ0058, "How often did you eat rice or other cooked grains (such as bulgur, cracked wheat, or millet)?"

Table 4.7. Frequency of Consumption of Rice and Other Cooked Grains by Ethnicity

Frequency (% of respondents) of consumption of rice and other cooked cereals	All	Mexican-American	Other Hispanic	White Non-Hispanic	Black Non-Hispanic	Other (incl Asian and multi-racial)
Never	9.4	5.7	3.6	10.4	9.5	5.5
1-6 times per year	11.1	5.4	3.7	12.5	9	10.1
7 -11 times per year	9.9	6.2	3.2	11	9.8	5
1 time per month	10.2	6.4	4.2	12	7.1	3.1
2-3 times per month	20	17.3	9.5	21.6	19.3	10.5
1 time per week	12.8	16.3	14.9	13.4	10.3	4.4
2 times per week	13.2	20.6	16.3	11.9	15.9	9.3
3-4 times per week	7.5	13.9	22.6	5	11.9	12
5-6 times per week	2.3	5.2	10.2	0.9	4.6	7.4
1 time per day	2	2.1	8.5	0.7	2	15.3
2 or more times per day	1.4	0.5	3.2	0.3	0.7	17.3

Data source: National Health and Nutrition Examination Survey (NHANES), 2003-2004 and 2005-2006, Food Frequency Questionnaire question FFQ0058, "How often did you eat rice or other cooked grains (such as bulgur, cracked wheat, or millet)?" NHANES analytic guidelines (Johnson *et al.*, 2013) indicate that Mexican-Americans and Other Hispanics were under-represented in these surveys, and that the data should not be used to characterize intakes by these populations; data are provided here only as an indication that frequency of rice consumption varies by ethnic group.

4.4 EXPOSURE TO INORGANIC ARSENIC FROM RICE

4.4.1 RESULTS OF THE CURRENT STUDY

Data on intakes of rice (per capita per day and per eating occasion) generated based on NHANES/WWEIA results were combined with data on inorganic arsenic concentrations in rice to generate estimates of exposure to inorganic arsenic from rice consumption. In addition, mean per capita exposures to inorganic arsenic from rice were estimated by month for infants and children and for each year of life for the total population, in order to characterize inorganic-arsenic exposures from rice at different life stages. Results on rice intakes per kg bw are shown

in Tables 4.8 – 4.10 (mean per capita daily inorganic arsenic exposure) and Tables 4.11 – 4.13 (mean per-eating-occasion inorganic arsenic exposure). A review of the literature on intakes of inorganic arsenic from rice is presented in Appendix 9.12.

On the per capita basis, infants (less than 1 year of age) were exposed to 69 ng inorganic arsenic/kg bw/day from intake of infant rice cereals, and 94.1 ng inorganic arsenic/kg bw/day from all rice sources (Table 4.8). Most of this intake was from white-rice products. Per capita, males and females 0 – 6 years were exposed to 54.4 ng inorganic arsenic/kg bw/day from rice, including 48.0 ng/kg bw/day from white rice and 7.1 ng/kg bw/day from brown rice (Table 4.9). Males and females 0 – 50 years were exposed to 31.9 ng inorganic arsenic/kg bw/day from rice, including 28 ng/kg bw/day from white rice and 4.4 ng/kg bw/day from brown rice (Table 4.10).

Table 4.8. Mean per Capita Inorganic Arsenic Exposure from Infant Rice Cereal and from All Rice Grain and Rice Products: Males and Females Less Than 1 Year of Age

Mean per Capita Intake of Rice from Infant Rice Cereal[a,b]	Mean per Capita Intake of Inorganic Arsenic from Rice Cereal	Mean per Capita Intake of Rice Grain and Rice Products[a,b]	Mean per Capita Intake of Inorganic Arsenic from Rice Grain and Rice Products
g/kg bw/day	ng/kg bw/day	g/kg bw/day	ng/kg bw/day
0.664	69.0	0.925	94.1

[a] Data sources for inorganic arsenic (iAs) concentration: FDA (2013) and Consumer Reports (2012); ppb = ng iAs/g rice or µg iAs/kg rice

[b] Rice grain and rice products include infant rice cereal. Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.1. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates.

Table 4.9. Mean per Capita Inorganic Arsenic Exposure from Rice Grain and Rice Products: Males and Females, 0 – 6 years

Rice Type	Mean Inorganic Arsenic Concentration[a] ppb[b]	Mean per capita rice intake[c] g/kg bw/day	Mean per capita inorganic arsenic exposure from rice[d] ng/kg bw/day
All (Brown + White)	96.0	0.566	54.4
All Brown[e]	153.8	0.046	7.1
All White[e]	92.3	0.520	48.0
Brown Basmati[f]	133.3	0.007	0.9
Brown Jasmine[f]	142.4	0.001	0.1
Brown Instant/pre-cooked[f]	72.0	0.002	0.1
Brown Parboiled[f]	191.3	0.005	1.0
Brown Long/med/short grain, regular[f]	156.5	0.024	3.8
White Basmati[f]	62.3	0.010	0.6
White Jasmine[f]	75.1	0.050	3.8
White Instant/pre-cooked[f]	57.6	0.012	0.7
White Parboiled[f]	112.4	0.044	5.0
White Long grain, regular[f]	102.0	0.205	20.9
White Medium grain, regular[f]	81.5	0.102	8.4
White Short grain, regular[f]	78.9	0.014	1.1

[a] Data sources for inorganic arsenic (iAs) concentrations: FDA (2013), FDA (2016) and Consumer Reports (2012). The mean arsenic concentration for all rice was developed with the market-share estimates presented in Appendix 9.7.

[b] ppb = ng iAs/g rice or µg iAs/kg rice

[c] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2009-2010. Food codes included in analysis are listed in Appendix 9.9.1. The survey-based mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert his/her intake per day to intake per kg bw/day. The market-share mean rice intakes were developed using industry data (see Appendix 9.7). Note that the estimated intake for All Brown (resp. All White) is not equal to the sum of the individual brown (resp white) rices as 15.7% of rice consumption could not be attributable to any of these rice products (see Table 4.4)

[d] Calculated as: (ng iAs/g rice) * g rice/kg bw/day = ng iAs/kg bw/day.

[e] Subgroups by NHANES Survey Category

[f] Subgroups by Market Share Survey Category

Table 4.10. Mean per Capita Inorganic Arsenic Exposure from Rice Grain and Rice Products: Male and Females, 0 – 50 years

Rice Type	Mean Inorganic Arsenic Concentration[a] ppb[b]	Mean per capita rice intake[c] g/kg bw/day	Mean per capita inorganic arsenic exposure from rice[d] ng/kg bw/day
All (Brown + White)	96.0	0.332	31.9
All Brown[e]	153.8	0.029	4.4

Rice Type	Mean Inorganic Arsenic Concentration[a] ppb[b]	Mean per capita rice intake[c] g/kg bw/day	Mean per capita inorganic arsenic exposure from rice[d] ng/kg bw/day
All White[e]	92.3	0.303	28.0
Brown Basmati[f]	133.3	0.004	0.6
Brown Jasmine[f]	142.4	<0.001	0.1
Brown Instant/pre-cooked[f]	72.0	0.001	0.1
Brown Parboiled[f]	191.3	0.003	0.6
Brown Long/med/short grain, regular[f]	156.5	0.015	2.4
White Basmati[f]	62.3	0.006	0.4
White Jasmine[f]	75.1	0.029	2.2
White Instant/pre-cooked[f]	57.6	0.007	0.4
White Parboiled[f]	112.4	0.026	2.9
White Long grain, regular[f]	102.0	0.120	12.2
White Medium grain, regular[f]	81.5	0.060	4.9
White Short grain, regular[f]	78.9	0.008	0.66

[a] Data sources for inorganic arsenic (iAs) concentrations: FDA (2013), FDA (2016) and Consumer Reports (2012). The mean arsenic concentration for all rice was developed with the market share estimates presented in Appendix 9.7.

[b] ppb = ng iAs/g rice or µg iAs/kg rice

[c] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2009-2010. Food codes included in analysis are listed in Appendix 9.9.1. The survey-based mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert his/her intake per day to intake per kg bw/day. The market-share mean rice intakes were developed using industry data (see Appendix 9.7). Note that the estimated intake for All Brown (resp. All White) is not equal to the sum of the individual brown (resp white) rices as 15.7% of rice consumption could not be attributable to any of these rice products (see Table 4.4)

[d] Calculated as: (ng iAs/g rice) * g rice/kg bw/day = ng iAs/kg bw/day.

[e] Subgroups by NHANES Survey Category

[f] Subgroups by Market Share Survey Category

To put exposure to inorganic arsenic from rice into perspective, we plotted exposures to inorganic arsenic from rice, water, and apple juice by age (Figure 4.6). Inorganic arsenic exposures from rice and drinking water are approximately equal on the kg bw basis through 50 years of age, when inorganic arsenic is present in water at 2 ppb. Exposures to inorganic arsenic from rice and apple juice are approximately equal at age 1, but apple juice then declines in importance as a source of inorganic arsenic exposure.

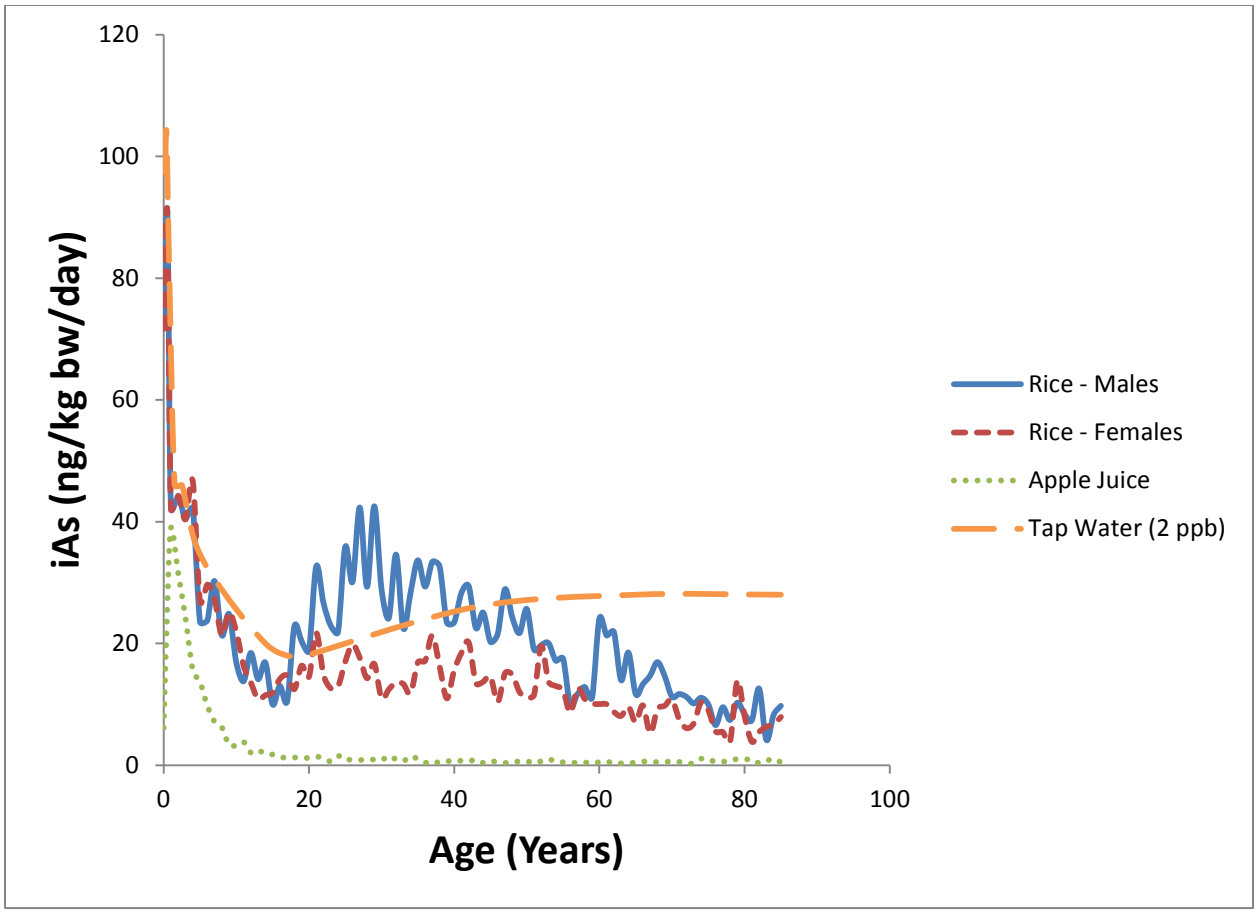

Figure 4.6. Mean per Capita Daily Inorganic Arsenic Intake from Rice (Grain and Products), Apple Juice, and Tap Water, by Age and Gender

Data source for inorganic arsenic (iAs) concentrations: FDA (2013) and Consumer Reports (2012).
Data source for rice and apple juice consumption estimates: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2010. Food codes included in analysis are listed in Appendix 9.9.1. Mean rice and iAs intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert his/her intake per day to intake per kg bw/day.
Data source for water-intake estimates: EPA (2011).

As shown in Table 4.7, rice intake varies based on ethnicity, with 32.6% of individuals in the "other" ethnic group, which includes Asians and multi-racial individuals, consuming rice or other cooked grains at least once a day. We estimated exposure to inorganic arsenic per rice-eating occasion to allow estimation of risks from rice consumption for frequent consumers in these and other population groups (Tables 4.11 and 4.12).

Based on the assumptions used in this study, infants were exposed to about 133.9 ng/kg bw inorganic arsenic from each brown-rice eating occasion and 116.9 ng/kg bw inorganic arsenic from each white-rice eating occasion (Table 4.11). For ages 0 – 6 years (Table 4.12), estimated per eating occasion intake of inorganic arsenic was greatest for parboiled white rice (217 ng/kg

bw/eating occasion); for ages 0 – 50 years (Table 4.13), estimated per eating occasion intake of inorganic arsenic was greatest for parboiled brown rice (166 ng/kg bw/eating occasion).

Table 4.11. Mean Inorganic Arsenic Exposure from Infant Rice Cereal per Eating Occasion: Males and Females Less Than 1 Year of Age

Rice Cereal Type	Mean Inorganic Arsenic Concentration[a] ppb[b]	Mean Rice Cereal Intake[c] g/kg bw/eating occasion	Mean Inorganic Arsenic Exposure from Rice Cereal[d] ng/kg bw/eating occasion
Brown	119.0	1.125	133.9
White	103.9	1.125	116.9

[a] Data sources for inorganic arsenic (iAs) concentration: FDA (2013), FDA (2016) and Consumer Reports (2012)

[b] ppb = ng iAs/g rice or µg iAs/kg rice

[c] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert his/her intake per day to intake per kg bw/eating occasion.

[d] Calculated as: (ng iAs/g rice) * g rice/kg bw/eating occasion = ng iAs/kg bw/eating occasion.

Table 4.12. Mean Inorganic Arsenic Exposure from Rice per Eating Occasion: Males and Females, 0 – 6 years

Rice Type	Mean Inorganic Arsenic Concentration[a] ppb[b]	Mean rice intake[c] g/kg bw/eating occasion	Mean inorganic arsenic exposure[d] ng/kg bw/eating occasion
Brown Basmati	133.3	1.01	134.7
Brown Jasmine	142.4	1.01	143.9
Brown Instant/pre-cooked	72.0	1.01	72.7
Brown Parboiled	191.3	1.01	193.3
Brown Long/med/short grain, regular	156.5	1.01	158.1
White Basmati	62.3	1.929	120.2
White Jasmine	75.1	1.929	144.8
White Instant/pre-cooked	57.6	1.929	111.0
White Parboiled	112.4	1.929	216.8
White Long grain, regular	102.0	1.929	196.7
White Medium grain, regular	81.5	1.929	157.3
White Short grain, regular	78.9	1.929	152.1

[a] Data sources for inorganic arsenic (iAs) concentrations: FDA (2013) and Consumer Reports (2012); ppb = ng iAs/g rice or µg iAs/kg rice.

[b] ppb = ng iAs/g rice or µg iAs/kg rice

[c] Calculated as: (ng iAs/g rice) * g rice/kg bw/eating occasion = ng iAs/kg bw/eating occasion.

[d] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in

population-response rates. The body weight of each NHANES respondent was used to convert his/her intake per day to intake per kg bw/eating occasion.

Table 4.13. Mean Inorganic Arsenic Exposure from Rice per Eating Occasion: Males and Females, 0 – 50 years

Rice Type	Mean Inorganic Arsenic Concentration[a] ppb[b]	Mean rice intake[c] g/kg bw/eating occasion	Mean inorganic arsenic exposure[d] ng/kg bw/eating occasion
Brown Basmati	133.3	0.866	115.5
Brown Jasmine	142.4	0.866	123.4
Brown Instant/pre-cooked	72.0	0.866	62.3
Brown Parboiled	191.3	0.866	165.7
Brown Long/med/short grain,	156.5	0.866	135.5
White Basmati	62.3	1.094	68.2
White Jasmine	75.1	1.094	82.1
White Instant/pre-cooked	57.6	1.094	63.0
White Parboiled	112.4	1.094	123.0
White Long grain, regular	102.0	1.094	111.5
White Medium grain, regular	81.5	1.094	89.2
White Short grain, regular	78.9	1.094	86.3

[a] Data sources for inorganic arsenic (iAs) concentrations: FDA (2013) and Consumer Reports (2012).

[b] ppb = ng iAs/g rice or µg iAs/kg rice

[c] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert his/her intake per day to intake per kg bw/eating occasion.

[d] Calculated as: (ng iAs/g rice) * g rice/kg bw/eating occasion = ng iAs/kg bw/eating occasion.

4.5 BIOAVAILABILITY AND BIOACCESSIBILITY OF INORGANIC ARSENIC IN RICE

The characterization of the toxicity of inorganic arsenic is largely based on epidemiological studies of populations exposed to high concentrations of arsenic in drinking water. Because arsenic in rice must be solubilized by digestion before it can be absorbed, the amount of ingested arsenic that is transferred to systemic circulation from rice intake may be the same or less than that from water intake. Several *in vivo* and *in vitro* studies have been conducted to address this issue of arsenic bioavailability. Juhasz *et al.* (2006) conducted a bioavailability study with pigs given organic and inorganic arsenic species, either in solution (by gavage) or in cooked rice, and compared the amount of arsenic in blood with the level after intravenous administration of the same amount of organic and inorganic arsenic species. While inorganic arsenic species were completely absorbed when given in solution (by gavage), organic species were absorbed at a

much lower rate (17% for MMA and 33% for DMA). The bioavailability of two different cooked rice samples was also examined. The first, in which rice was grown under glasshouse conditions with arsenic-contaminated irrigation water, resulted in grain with arsenic predominantly speciated in the form of DMA (86%). Bioavailability of mostly DMA from this rice sample was 33%; about the same as biovailability from pure DMA given by gavage. The second rice sample had elevated inorganic arsenic levels resulting from cooking the rice in water with 1,000 µg/L inorganic arsenic. The relative bioavailability of this rice sample containing inorganic arsenic was about 89% (±9%).

He and Zheng (2010) conducted a mass balance study on the bioaccessibility of total arsenic with two human subjects, in which the amount of arsenic excreted in the urine was compared with the amount consumed from dietary exposure. Arsenic excretion was first measured in each subject over a 5-day period consisting of a non-rice diet with lower levels of arsenic (10-15 µg/day), and then again for a second 5-day period consisting of a rice-based diet containing higher levels (about 35 µg/day). The contribution from drinking-water and fish was negligible for both diets. The amount of increased arsenic excreted in the urine, largely as DMA, was estimated to be 58% for one subject and 69% for the other. However, the authors noted that actual bioavailability is likely to be somewhat higher, as some of the arsenic entering systemic circulation may be eliminated through hair and skin. In addition, 24% of the total arsenic in the rice was inorganic. If only 33% of the organic arsenic is absorbed (the value from Juhasz *et al.*, 2006), the estimated absorption of inorganic arsenic for each of the two subjects was 66% and 80%, respectively.

Several studies have also been conducted on the bioaccessibility of arsenic in rice *in vitro,* using artificial digestion systems. Although these studies are not useful for estimating the amount of arsenic that enters systemic circulation, they do provide information about the release of bound arsenic from rice under various conditions (Laparra *et al.*, 2005; He *et al.*, 2012; Horner and Beauchemin, 2012; Signes-Pastor *et al.*, 2012; Sun *et al.*, 2012; Horner and Beauchemin, 2013)

In summary, the available evidence indicates that most of the arsenic in rice is released and absorbed. Based on *in vivo* experiments, the bioavailability of inorganic arsenic in rice is assumed to be between 70% and 90% in this risk assessment (see Section 5.1).

4.6 CONCLUSIONS REGARDING EXPOSURE TO INORGANIC ARSENIC FROM RICE

This assessment of exposure to inorganic arsenic from rice and rice products provides important data on inorganic arsenic concentrations in rice products consumed by the U.S. population, on average rice intakes (per day and per eating occasion) by U.S. subpopulations, and on estimated exposure of U.S. subpopulations to inorganic arsenic from rice. The assessment showed that

infants less than 1 year of age have a per capita inorganic arsenic exposure higher than per capita exposures for the other population groups (94.1 ng/kg bw/day vs. 54.4 ng/kg bw/day for 0 – 6 years and 31.9 ng/kg bw/day for 0 – 50 years). The assessment also provides important data on inorganic arsenic exposures per eating occasion, allowing estimation of daily inorganic arsenic exposures by populations that typically consume multiple portions of rice on a daily basis. For example, 17.3% of individuals with race ethnicity categorized as "other" (other than Hispanic, Black, or White) reported consuming rice two or more times per day. The exposure to inorganic arsenic ranged from 62.4 to 216.8 ng/kg bw/eating occasion, depending on the type of rice and age range; therefore, the 17.3% of individuals in the "other" race-ethnicity group who reported consuming rice two or more times per day could be consuming 435 ng inorganic arsenic/kg bw/day, or more, on a daily basis. The review of literature on bioavailability of inorganic arsenic indicates that this arsenic is highly bioavailable (70% – 90% absorption).

While this exposure assessment helps to fill data gaps regarding exposures to inorganic arsenic from rice, there are a number of limitations that must be recognized. There are uncertainties related to the analysis of inorganic arsenic concentrations in rice grain and in infant cereals, due to the relatively small number of samples analyzed for some product types; the number of samples analyzed for some product types was only one (brown parboiled rice) or two (brown instant rice). Because the sampling plan was not based on market shares of major brands and was not statistically designed to reflect availability of different products across the United States, the extent to which the samples analyzed are representative of rice consumed is unknown. In addition, for the purposes of the exposure assessment, the inorganic arsenic concentrations measured in rice grain were assumed to be representative of inorganic arsenic concentrations in rice present as an ingredient in processed rice products, such as rice crackers, rice cakes, and rice beverage. Intake of rice by adults may be overestimated, due to EPA's assumption that all beer contains rice as an ingredient. Finally, because the NHANES/WWEIA data provided information on whether individuals consumed white or brown rice, but did not distinguish between different types of rice (e.g,. jasmine rice, basmati rice), intakes of specific types of rice were estimated using market-share data, and the results may not reflect the intakes of specific types of rice by the NHANES/WWEIA survey populations included in the exposure assessment. Further research is needed to supplement the database of values on concentrations of inorganic arsenic in specific rice products and to provide data on usual daily intakes of specific types of rice by individuals.

4.7 EXPOSURE TO MMA AND DMA FROM RICE AND INFANT RICE CEREAL

Results from FDA's arsenic speciation study (FDA, 2013 and 2016; Appendix 9.5) in various types of rice and rice products showed a low MMA content. The mean MMA concentration range across rice and rice products was < 3 ppb (non-detect) to 12 ppb; the highest mean MMA level was 7 ppb in rice grain and 5 ppb in infant rice cereal. The mean DMA concentration

ranged from 32 to 131 ppb in rice grain and 7 to 123 ppb in rice products, respectively. Infant rice cereal contained a mean of 52 ppb DMA. There is no correlation between the concentration of MMA and/or DMA and the concentration of inorganic arsenic, with the percentage of inorganic arsenic varying from 12 to 100% in the rice analyzed. Because of the large variation in MMA and DMA concentrations and lack of correlation with inorganic arsenic concentration, both within and between products, the average MMA and DMA values are not appropriate for evaluating arsenic species distribution within or between product types.

Based on the consumption estimates and the highest mean DMA concentrations found in rice and rice products, mean per capita DMA exposures are calculated for 1) infants less than 1 year of age, from infant rice cereal, 2) children from 0 – 6 years of age, from rice grain, and 3) from 0 – 50 years of age, from rice grain. The results of mean per capita exposure on the basis of both daily and one eating occasion are presented in Tables 4.14 and 4.15 below.

Table 4.14. Mean per Capita DMA Exposure for U.S. Life Stages, from Infant Rice Cereal and Rice

Population Subgroup	Rice Type	Mean DMA Concentration[a] (ppb)	Mean Intake of Infant Rice Cereal or Rice[b] (g/kg bw/day)	Mean DMA Exposure[c] (ng/kg bw/day)
< 1 year	Infant rice cereal	52	0.664	34.5
0 – 6 years	All rice[d]	131	0.566	74.1
0 – 50 years	All rice[d]	131	0.332	43.5

[a] Data source for DMA concentrations: FDA (2013, 2016). ppb = ng DMA/g rice

[b] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2010 for < 1 year and 2009-2010 for 0-6 years and 0-50 years. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates.

[c] Calculated as mean DMA concentration in ppb: (ng DMA/g rice) * g rice/kg bw/day.

[d] Mean DMA Concentration used is the highest mean across all rice categories which is for long grain white rice.

Table 4.15. Mean per Capita DMA Exposure for U.S. Life Stages, per Eating Occasion, from Infant Rice Cereal and Rice

Population Subgroup	Rice Type	Mean DMA Concentration[a] (ppb)	Mean Intake of Infant Rice Cereal or Rice[b] (g/kg bw/eating occasion)	Mean DMA Exposure[c] (ng/kg bw/eating occasion)
< 1 year	Infant rice cereal	52	1.125	58.5
0 - 6 years	Brown	119	1.010	120.2
0 - 6 years	White[d]	131	1.929	252.7
0 - 50 years	Brown	119	0.866	103.1
0 - 50 years	White[d]	131	1.094	143.3

[a] Data source for DMA concentrations: FDA (2013, 2016). ppb = ng DMA/g rice
[b] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2010 for < 1 year and 2009-2010 for 0-6 years and 0-50 years. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates.
[c] Calculated as mean DMA concentration in ppb (ng DMA/g rice) * g rice/kg bw/day.
[d] Mean DMA Concentration for white rice used the highest mean across white rice categories which is for long grain white rice.

A literature search, including the three most recent extensive reviews of arsenic by national and international organizations (ATSDR/CDC, EFSA and WHO-FAO), revealed that only ATSDR/CDC (2007) has set an oral Minimal Risk Level (MRL) for chronic exposure to MMA and DMA. These chronic-duration oral MRLs are 0.01 mg/kg bw/day for MMA and 0.02 mg/kg bw/day for DMA. These MRLs are for exogenous MMA and DMA, not for exposure to DMA and/or MMA resulting from metabolism of inorganic arsenic.

Table 4.14 describes the mean per capita daily exposure to DMA from rice or infant rice cereal as ranging from 43.5 to 74.1 ng/kg bw/day. The highest exposure of 74.1 ng/kg bw/day is for children from birth through 6 years of age. This level of DMA exposure corresponds to 0.4% of the MRL of 0.02 mg/kg bw/day.

Similarly, as shown in Table 4.15, the mean per eating occasion exposure to DMA from rice or infant rice cereal ranges from 87 to 253 ng/kg bw/eating occasion. The highest exposure of 253 ng/kg bw/eating occasion is for children from birth through 6 years of age. This level of DMA exposure corresponds to 1.3% of the MRL.

Exposure to DMA from rice and rice products, as mean per capita or mean per eating occasion, does not pose a health concern, based on the ATSDR MRL value. The 2004 IARC monograph considered additional data to provide sufficient evidence of the carcinogenicity of the organo-arsenical, dimethylarsinic acid (DMA^V). DMA^V, a known biomethylation product in humans and rats, produced tumors in the urinary bladder of rats and lungs of mice (IARC, 2004).

The highest mean concentration of MMA found in rice (7 ppb) and infant rice cereal (5 ppb) is 19 (=131/7) and 15 (=77/5) folds lower than DMA concentration, respectively. Because the difference in the MRL values of MMA and DMA are relatively small, only two-fold, exposures to MMA from ingesting infant rice cereal or rice grain represent 0.04% MRL at mean per capita consumption level and 0.1% MRL at mean per eating occasion level, respectively. Therefore, exposure to MMA from rice grain and rice products does not likely pose a health concern.

5 RISK CHARACTERIZATION OF LUNG AND BLADDER CANCER

This section provides the baseline predictions for lifetime cancer risk from dietary exposure to inorganic arsenic in rice grain and rice products (food containing rice as an ingredient). The risk model estimates lung and bladder cancer developed over a lifetime for three periods of exposure: (1) exposure only during infancy, (2) exposure only during childhood, and (3) exposure from birth to adulthood. In addition, results of several scenarios that predict the impact of mitigations meant to reduce the incidence of lung and bladder cancer are presented.

5.1 DESCRIPTION OF THE RISK MODEL

We determined the predicted risk of cancer from exposure to inorganic arsenic in rice and rice products by integrating the dose-response model and the exposure assessment, using a Monte-Carlo simulation model with a structure illustrated in Figure 5.1. For a given food (rice or rice product), the mean level of inorganic arsenic and its standard error was estimated from the measured concentration data (see Section 4). An uncertainty distribution of the mean level of inorganic arsenic in the food was derived from these statistics, using a normal distribution. This distribution was combined with the food intake for the population that was considered (point estimate of the average per capita consumption for per capita exposure - see Section 4) or with a specified quantity of food (for per eating occasion exposure) to provide the estimated intake of inorganic arsenic from this product. A bioavailability adjustment factor (uncertainty distribution – rectangular distribution 70 – 90%) was further applied to derive an uncertainty distribution of the bioavailable inorganic arsenic intake from the food. Each intake value was used in one of the 1,000 dose-response model iterations (see Section 3) that evaluated the relationship between the frequency of bladder and lung cancer, relative to dose. The median of the 1,000 iterations was used to provide the central estimate of the frequency of disease, and the 5^{th} and 95^{th} quantiles provided the uncertainty (90% confidence interval) of these estimates.

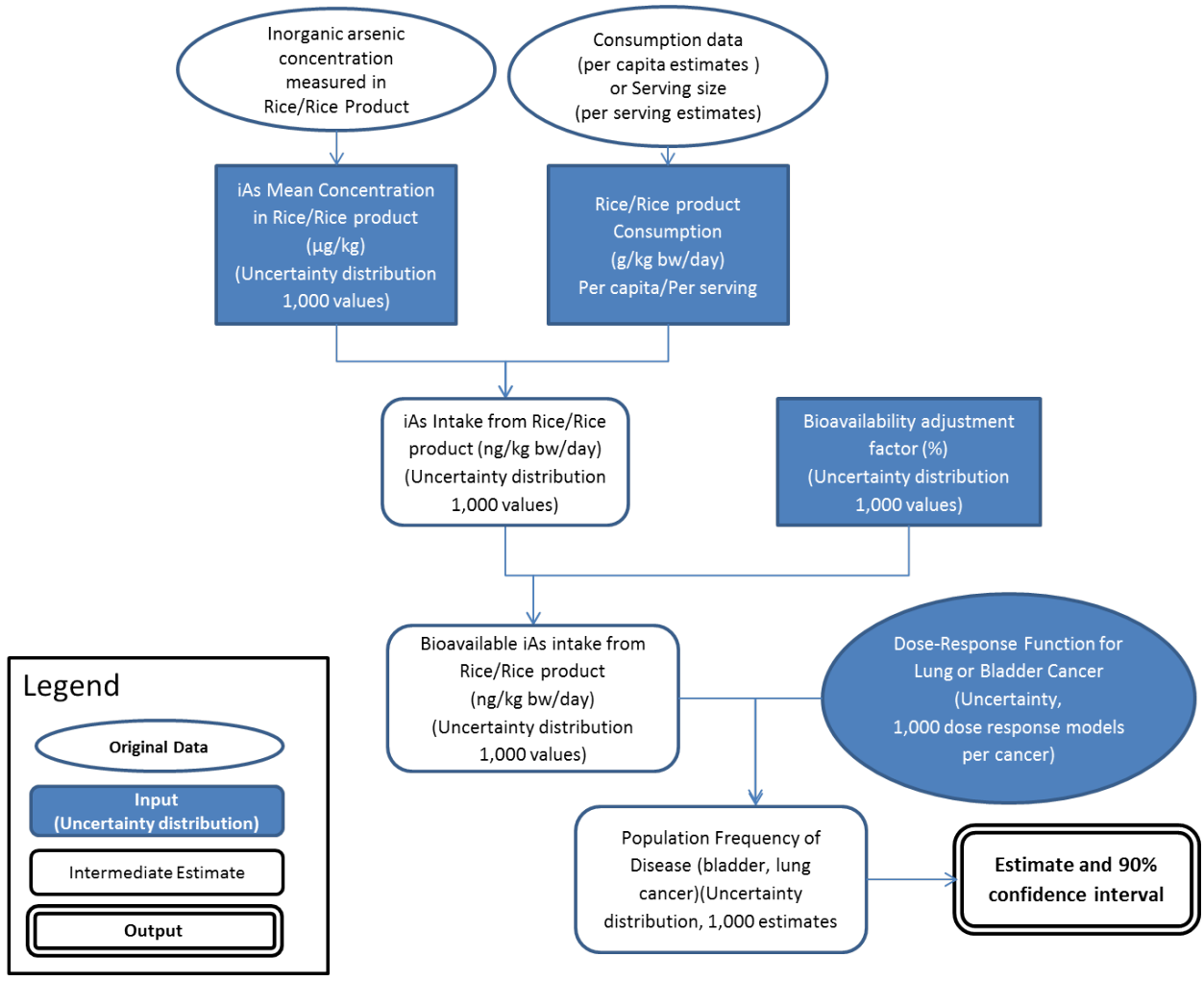

Figure 5.1 Interrelationship of the Risk Assessment Model Components

5.2 BASELINE RESULTS FOR POTENTIAL CARCINOGENIC EFFECTS

The baseline results provide an estimate of the current cancer risk from exposure to inorganic arsenic in rice and rice products. The estimates are provided for different food intake levels, life stages, and types of rice.

Risk estimates are provided in two forms, based on estimated food-intake amounts and resulting exposure levels:

- **Per capita** – the predicted cancer rate, based on the estimated average lifetime exposure to inorganic arsenic in rice among the total U.S. population (including consumers and non-consumers of rice). The per capita dose level includes the consumption of rice and products containing rice ingredients.

- **Per serving** (per eating occasion) – the predicted cancer rate, based on consumption of a specified quantity of rice once per day. The per eating occasion dose level is based on consuming rice grain alone (i.e., not including rice ingredients in other foods). As a result, the dose levels for "per serving" are considerably higher, compared with the per capita estimates.

The predicted lifetime cancer risk estimates are provided for three periods of chronic exposure (life stages):

- **Infants.** This estimate is based on exposure up to 1 year old (i.e., 1 year of exposure), and is calculated by multiplying the lifetime risk estimate by the percentage of exposure that occurs during this period. The estimate of cancer risk presumes no further exposure to inorganic arsenic from the consumption of rice and rice products after the age of 1.

- **Children.** This estimate is based on childhood exposure through the 6^{th} year of age (i.e., 7 years of exposure) and is calculated by multiplying the lifetime risk estimate by the percentage of exposure that occurs during this period. The estimate of cancer risk presumes no further exposure to inorganic arsenic from the consumption of rice and rice products after the age of 6.

- **Lifetime.** This estimates risk results from exposure over a lifetime, including childhood. There is evidence of an approximately 25-year latency period for development of cancer associated with inorganic arsenic exposure (Marshall *et al.*, 2007). We believe estimates utilizing an exposure period of 0 – 50 years of age is the most appropriate for a cancer risk assessment for arsenic.

Risk estimates are also provided for consumption of different types of rice grain and rice products that may contain different concentrations of inorganic arsenic. The rice commodities examined included the following.

- All rice grain and products containing rice grain as an ingredient, combined.
- Estimates for exposure to inorganic arsenic from brown and white rice grain separately, using the NHANES consumption patterns.
- Separate estimates for exposure to inorganic arsenic from a variety of different types of rice grain (e.g., basmati), using market-share data to estimate consumption patterns.

5.2.1 PER CAPITA ESTIMATES

Table 5.1 provides the predicted total (bladder and lung) lifetime cancer risk estimates, using the mean per capita exposure estimates (rice / product intake levels and the estimated concentration of inorganic arsenic) presented earlier, in Section 4. As might be expected, the predicted cancer-risk estimates are higher when exposure occurs for a longer period of time. Predicted cancer risk is 39 cases per million from lifetime (i.e., 50 years) exposure, compared with 2.3 cases per million from exposure during infancy (up to 1 year old) alone, and 9.1 cases per million from exposure during childhood (up through 6 years old) alone. The lifetime risk for all rice grain and rice products is predominately driven by consumption of white rice (34 cases per million), compared with brown rice (5.4 cases per million). Although brown rice contains, on average, higher levels of inorganic arsenic than does white rice (see Table 4.3 in Section 4), the per capita consumption levels are considerably higher for white rice (see Table 4.6 in Section 4). Within the white rice types, the risk differs; the highest risk was attributed to consumption of long-grain rice, compared with other types of rice. Assuming a U.S. population of 317 million, and an average life expectancy of 78.6 years, our estimate for the U.S. population, based on mean rice intake and exposure factor parameters, is 157 lung and bladder cancers, annually, associated with dietary inorganic arsenic intake from rice alone ((39 x 317)/78.6 = 157). Taking the 90% Confidence Interval (CI) into account, we are 90% confident that the true number of annual lung and bladder cancer cases (based on mean rice intake rates) is between 0 and 319 annual cases.

Table 5.1. Predicted Total Lifetime Cancer Risk (Bladder and Lung) Attributable to Inorganic Arsenic in Rice and Rice Products, by Exposure Period/Life Stage, Using Per Capita Consumption Estimates

Rice Type[a,b]	Median Estimated Total Cancer Cases Per Million (90% C.I.)[c] for Infants (< 1 year)	Median Estimated Total Cancer Cases Per Million (90% C.I.)[c] for Children (0 to 6 years)	Median Estimated Total Cancer Cases Per Million (90% C.I.)[c] for Lifetime (0 to 50 years)
All Rice Grain and Rice Products	2.3 (0, 4.6)	9.1 (0, 19)	39 (0, 79)
All White Rice	-	8.0 (0, 16)	34 (0, 69)
Infant WhiteRice Cereal	1.6 (0, 3.4)	N/A	N/A
All Brown Rice	-	1.2 (0, 2.4)	5.4 (0, 11)
Infant Brown Rice Cereal	1.9 (0, 3.9)	N/A	N/A
White Basmati	N/A	<1 (0, 0.2)	<1 (0, 0.9)

Rice Type[a,b]	Median Estimated Total Cancer Cases Per Million (90% C.I.)[c] for Infants (< 1 year)	Median Estimated Total Cancer Cases Per Million (90% C.I.)[c] for Children (0 to 6 years)	Median Estimated Total Cancer Cases Per Million (90% C.I.)[c] for Lifetime (0 to 50 years)
White Jasmine	N/A	<1 (0, 1.3)	2.7 (0, 5.5)
White Instant/Pre-cooked	N/A	<1 (0, 0.2)	<1 (0, 0.97)
White Parboiled	N/A	<1 (0, 1.7)	3.5 (0, 7.2)
White Long Grain, regular	N/A	3.5 (0, 7.2)	15 (0, 31)
White Medium Grain, regular	N/A	1.4 (0, 2.9)	5.9 (0, 12)
White Short Grain, regular	N/A	<1 (0, 0.4)	<1 (0, 1.7)
Brown Basmati	N/A	<1 (0, 0.3)	<1 (0, 1.4)
Brown Jasmine	N/A	<1 (0, 0.04)	<1 (0, 0.2)
Brown Instant/ Pre-Cooked	N/A	<1 (0, 0.04)	<1 (0, 0.2)
Brown Parboiled	N/A	<1 (0, 0.4)	<1 (0, 1.7)
Brown Long/Medium/ Short Grain, regular	N/A	<1 (0, 1.3)	2.9 (0, 6.0)

C.I. = confidence interval
N/A = not applicable. Market-share data are not relevant to infants < 1 year.
[a] White and brown rice grain were considered separately, using NHANES/WWEIA consumption-survey data to determine relative exposure.
[b] Types of white and brown rice were considered separately, using market-share data to determine relative exposure.
[c] Values presented are the median number of cancer cases per million, and in parentheses are 5% and 95% confidence limits based on per capita estimates. All risk estimates are lifetime. The age range reflects the risk that is attributable to exposure during that interval (life stage). .

5.2.2 PER SERVING (EATING OCCASION) ESTIMATES

Table 5.2 provides the predicted total (bladder and lung) lifetime cancer risk estimates, assuming one eating occasion per day for the entire exposure duration evaluated for each life stage, for different types of rice. To put it in perspective, these risk estimates are based on 365 eating

occasions for an infant, 2,555 eating occasions for a child (i.e., 365 days × 7 years) and 18,615 eating occasions for an adult (i.e., 365 days × 51 years).

For white-rice varieties, predicted cancer risk is highest for parboiled rice, at 149 cases per million for a lifetime of daily consumption (up to 50 years old) and 36 cases per million for exposure only during childhood (up through 6 years old). These risk estimates can be attributed to the higher average concentrations of inorganic arsenic in parboiled rice, which is most similar to brown rice. The predicted lifetime cancer risks for long-grain white rice, which has the largest market share (37%), is 136 cases per million for lifetime exposure and 33 cases per million for children. For brown-rice varieties, the highest predicted lifetime cancer risk also is for parboiled rice. However, there is significant uncertainty in these risk estimates, because they are based on a very small sample size of inorganic arsenic concentrations. In general, risk estimates are higher for brown rice than for white rice, due to the higher levels of inorganic arsenic in brown-rice varieties, relative to white-rice varieties. The lowest predicted risk estimates are for instant/pre-cooked white or brown rice, at 18 and 12 cases per million for children, respectively, and 74 cases per million for lifetime exposure, for both white and brown rice.

The predicted total cancer risks for infants (<1 year old) who consume white and/or brown rice cereal are 2.8 and 3.2 cases per million, respectively.

Table 5.2. Predicted Total (Bladder and Lung) Lifetime Cancer Risks Attributable to Inorganic Arsenic in Rice and Rice Products by Exposure Duration/Life Stage, Using One Eating Occasion per Day Estimates

Rice Type[a]	Median Estimated Total Cancer Cases Per Million (90% CI)[b,c] for Infants (< 1 year old)	Median Estimated Total Cancer Cases Per Million (90% CI)[b,c] for Children (0 – 6 years old)	Median Estimated Total Cancer Cases Per Million (90% CI)[b,c] for Lifetime (0 – 50 years)
Infant White Rice Cereal	2.8 (0, 5.7)	N/A[d]	N/A
White Basmati	N/A	20 (0, 41)	82 (0, 171)
White Jasmine	N/A	24 (0, 50)	99 (0, 205)
White Instant/Pre-cooked	N/A	18 (0, 38)	74 (0, 157)
White Parboiled	N/A	36 (0, 74)	149 (0, 307)
White Long Grain, regular	N/A	33 (0, 67)	136 (0, 278)
White Medium Grain,	N/A	26	108

Rice Type[a]	Median Estimated Total Cancer Cases Per Million (90% CI)[b,c] for Infants (< 1 year old)	Median Estimated Total Cancer Cases Per Million (90% CI)[b,c] for Children (0 – 6 years old)	Median Estimated Total Cancer Cases Per Million (90% CI)[b,c] for Lifetime (0 – 50 years)
regular		(0, 54)	(0, 222)
White Short Grain, regular	N/A	25 (0, 52)	104 (0, 216)
Infant Brown Rice Cereal	3.2 (0, 6.6)	N/A	N/A
Brown Basmati	N/A	22 (0, 46)	139 (0, 288)
Brown Jasmine	N/A	24 (0, 49)	147 (0, 307)
Brown Instant/ Pre-Cooked	N/A	12 (0, 25)	74 (0, 155)
Brown Parboiled	N/A	29 (0, 71)	184 (0, 444)
Brown Long/Medium/ Short Grain, regular	N/A	26 (0, 54)	165 (0, 339)

C.I. = confidence interval
N/A = not applicable. Infants consume rice cereal.
[a] Types of white rice were considered separately, using market-share data.
[b] All risk estimates are lifetime. The age range reflects the risk attributable to exposure during that interval.
[c] Values presented are the median number of cancer cases per million and in parentheses are 5% and 95% confidence limits based on per capita estimates.

5.2.3 COMPARISON OF FDA AND EPA MODEL ESTIMATES

A comparison of the predicted cancer-risk estimates, using FDA's dose-response model described in this report (see Section 3) and the EPA dose-response model (Morales *et al.*, 2000), is provided in Table 5.3. In general, the predicted total lung and bladder cancer risk is approximately 30% lower using the FDA dose-response model, compared with the EPA dose-response model. As described in Section 3, both the FDA and EPA dose-response models are similar for lung cancer, and, as shown in the table below, the resulting predicted lifetime risk of lung cancer is well aligned when using these two dose-response models. The predicted lifetime bladder cancer risk is lower using the FDA model, compared with the EPA model. The difference is primarily the result of the different assumptions and data for bladder cancer (see description provided in section 3.3).

In interpreting these data, it is important to consider that the median predicted cancer-risk estimates have significant uncertainty and correspondingly large confidence intervals (CI). For

example, the total EPA cancer risk estimate of 56 cases in one million for all rice grain and rice products is within the FDA 90% CI of 0 and 79. Likewise, the majority of the EPA risk estimates are also within the FDA 90% CI. However, the median FDA estimates are outside the EPA 90% CI. Overall, the EPA and FDA cancer-risk estimates are within the anticipated model uncertainty.

Table 5.3. Predicted Lifetime (0-50 years) Cancer Risks (Median Estimated Cancer Cases Per Million) Attributable to Inorganic Arsenic in Rice and Rice Products, (90% CI)

Rice Type[a]	FDA Model Bladder[b]	FDA Model Lung	FDA Model Total	EPA Model (Morales *et al.* 2000) Bladder	EPA Model (Morales *et al.* 2000) Lung	EPA Model (Morales *et al.* 2000) Total
Per Capita Consumption of All Rice grain and Rice Products	10 (0, 39)	29 (0, 56)	39 (0, 79)	28 (23, 33)	29 (24, 35)	56 (48, 66)
Per Capita Consumption of White Rice	8.4 (0, 34)	25 (0, 49)	34 (0, 70)	24 (20, 29)	25 (21, 30)	50 (42, 58)
Per Capita Consumption of Brown Rice	1.3 (0, 5)	4 (0, 8)	5.4 (0, 11)	3.9 (3, 5)	4 (3, 5)	7.9 (6.7, 9)
White Basmati – One Eating Occasion per Day	20 (0, 83)	61 (0, 121)	82 (0, 171)	59 (48, 73)	62 (49, 75)	120 (101, 143)
White Jasmine – One Eating Occasion per Day	24 (0, 99)	73 (0, 145)	99 (0, 205)	71 (58, 87)	74 (59, 90)	145 (122, 172)
White Instant/Pre-cooked – One Eating Occasion per Day	19 (0, 77)	55 (0, 114)	74 (0, 157)	54 (40, 72)	57 (42, 74)	111 (84, 143)
White Parboiled – One Eating Occasion per Day	37 (0, 150)	110 (0, 216)	149 (0, 307)	106 (88, 130)	111 (90, 134)	217 (185, 256)
White Long Grain, regular – One Eating Occasion per Day	33 (0, 138)	100 (0, 196)	136 (0, 278)	96 (80, 117)	101 (82, 121)	197 (169, 231)
White Medium Grain, regular – One Eating Occasion per Day	27 (0, 109)	80 (0, 157)	108 (0, 222)	77 (64, 94)	81 (65, 97)	158 (134, 186)
White Short Grain, regular – One Eating Occasion per Day	26 (0, 104)	77 (0, 152)	104 (0, 216)	74 (61, 92)	78 (63, 94)	152 (129, 180)
Brown Basmati – One Eating Occasion per Day	34 (0, 141)	101 (0, 207)	138 (0, 287)	100 (78, 126)	104 (81, 129)	204 (165, 251)
Brown Jasmine – One Eating Occasion per Day	36 (0, 150)	107 (0, 221)	147 (0, 306)	106 (81, 136)	111 (85, 141)	218 (171, 274)
Brown Instant/ Pre-Cooked – One Eating Occasion per Day	18 (0, 76)	54 (0, 111)	74 (0, 155)	54 (41, 69)	56 (43, 71)	110 (88, 138)
Brown Parboiled – One Eating Occasion per Day	47 (0, 213)	135 (0, 318)	183 (0, 443)	142 (80, 213)	148 (82, 223)	290 (164, 436)
Brown Long/Medium/Short, regular – One Eating Occasion per Day	40 (0, 167)	122 (0, 237)	164 (0, 338)	117 (97, 142)	123 (100, 147)	239 (204, 281)

C.I. = confidence interval

[a] White and brown rice grain were considered separately, using NHANES consumption-survey data.

[b] Values presented are the median number of cancer cases per million, and in parentheses are 5% and 95% confidence limits based on cancer risk estimates i.e., the 90% CI.

5.3 "WHAT IF" SCENARIOS FOR CANCER RISKS

The baseline results provided in Section 5.2 are intended to estimate current lifetime cancer risks for the U.S. population from exposure to inorganic arsenic in rice and rice products.

That section described the predictions of the incidence of lung and bladder cancer based on current knowledge of dose-response and exposure (including the concentration of inorganic arsenic in rice grain and rice products, the frequency of consumption of rice and rice products, and amounts consumed per eating occasion). This risk assessment model can be used to estimate the likely impact of control measures, interventions, or mitigation strategies by changing one or more input parameters and measuring the change in the model outputs/risk estimates. These changes to the model, commonly referred to as "what if" scenarios, can be used to evaluate the likely impact of new mandatory or voluntary actions and/or new consumer exposure patterns on the predicted disease incidence. These "what if" scenarios can also be hypothetical, not necessarily reflecting achievable changes, but designed instead to show how different components of the model interact. Modeling specific scenarios can also assist in the interpretation of a complex risk-assessment model by allowing a comparison of baseline calculations to new situations. The following scenarios simulate the consequences (lifetime lung and bladder cancer risk) from a variety of changes in exposure, including:

1) Impact of establishing mandatory or voluntary limits for rice grain

2) Impact of limiting exposure during certain life stages

3) Impact of changing consumers' preparation practices

4) Impact of changing frequency of consumption and amounts consumed per eating occasion

5.3.1 MANDATORY OR VOLUNTARY LIMITS

These scenarios estimate the impact on cancer risk of establishing mandatory or voluntary limits for levels of inorganic arsenic in rice and rice products. In conducting these scenarios, we presumed that no products above the specified limit enter the U.S. food supply and that the predicted cancer risk would be reduced in proportion to the exposure. This scenario assumed that

the available contamination data (see Section 4 and Appendix 9.5) reflects the concentration range for inorganic arsenic in rice and rice products in the food supply. This assumption could under- or over-estimate the risk, depending on the actual changes in the food supply, following the implementation of a limit.

Table 5.4 provides the estimated percentage of rice and rice products expected to be above different mandatory or voluntary limits (from 50 to 200 ppb), based on the levels observed in the FDA (2013, 2016) and Consumer Reports (2012) surveys. As shown in Appendix 9.5, the levels of inorganic arsenic in rice and rice products ranged from <1 to 545 ppb, and the average for rice grain ranged from 59 ppb (instant) to 160 ppb (brown rice). Table 5.5 provides the average concentration of inorganic arsenic in rice, after any samples above the specified limit are removed. These values were used to estimate the percentage risk reduction from decreased iAs content in rice reported in Table 5.6.

Table 5.4. Estimated Percentage of Market Above Specified Limit (in %)

Rice Type	200 ppb	150 ppb	100 ppb	75 ppb	50 ppb
Brown, Basmati	6	25	75	94	100
Brown, Infant Cereal	7.7	24.6	53.8	84.6	95.4
Brown, Long/Medium/Short grain	15.8	55.8	93.3	99.2	99.2
White, Basmati	0	0	10.3	21.2	46.3
White, Infant Cereal	0	1.1	62.0	91.3	98.9
White, Instant	0	0	7.1	14.3	42.9
White, Jasmine	0	0	4.3	47.8	91.3
White, Parboiled	0	9.1	68.2	95.5	100
White, Long grain	0	7.5	45.7	89.6	99.4
White, Medium grain	0	1.1	26.6	57.4	94.7
White, Short grain	0	0	13	56.5	100

Note: Levels of inorganic arsenic in Rice Type categories can be found in Table 4.3 in Section 4.2.4; ppb = µg/kg

Table 5.5. Average Concentration (ppb) of Samples Below Specified Limit

Rice Type	200 ppb	150 ppb	100 ppb	75 ppb	50 ppb
Brown, Basmati	128.2	110.5	81.8	66.0	N/A
Brown, Infant Cereal	110.5	95.4	79.0	55.3	39.5
Brown, Long/Medium/Short grain	144.2	121.1	82.4	33.6	33.6
White, Basmati	62.3	62.3	56.7	49.2	40.5
White, Infant Cereal	103.9	103.4	83.5	60.6	20.8

Rice Type	200 ppb	150 ppb	100 ppb	75 ppb	50 ppb
White, Instant	57.6	57.6	51.7	48.0	40.2
White, Jasmine	75.1	75.1	73.5	62.6	40.7
White, Parboiled	112.4	107.0	91.5	71.9	N/A
White, Long grain	102.0	97.0	83.3	63.9	23.3
White, Medium grain	81.5	80.5	70.8	58.2	45.2
White, Short grain	78.9	78.9	75.4	63.1	N/A

N/A = not applicable. All samples above 50 ppb. ppb = µg/kg

Table 5.6 provides the relative cancer risk reduction estimated from implementation of a variety of specified limits (50 to 200 ppb). A limit of 300 ppb would not have any predicted impact on cancer risk, because it would not result in removal of any samples from the food supply (i.e., concentration data are below this level, currently). A limit of 200 ppb would have nominal reduction (approximately 11% or less) in estimated risk, primarily for brown rice and infant cereal made with brown rice. A limit of 100 ppb or 150 ppb would have a moderate impact on risk reduction. A limit of 75 ppb would have considerable impact on risk reduction for all types of rice (from approximately 16% to 78%). Limits of 50 ppb and 75 ppb were estimated to have significant reduction in the predicted risk of lung and bladder estimates, compared with the baseline. An exception is that no risk reduction is calculated for a 50 ppb limit for some products (brown basmati, , parboiled white rice, short grain white rice), because all of the concentration data available were above the limit (50 ppb).

Table 5.6. Percentage Risk Reduction from a Variety of Mandatory or Voluntary Limits (in %)

Rice Type	200 ppb	150 ppb	100 ppb	75 ppb	50 ppb
Brown, Basmati	4	17	39	51	N/A
Brown, Infant Cereal	11	21	37	54	68
Brown, Long/Medium/Short grain	7.8	22.6	47.3	78.5	78.5
White, Basmati	0	0	9	21	35
White, Infant Cereal	0	0	18.8	41.3	79.4
White, Instant	0	0	10.2	16.6	30.2
White, Jasmine	0	0	2.1	16.7	45.8
White, Parboiled	0	4.8	18.6	36.1	N/A
White, Long grain	0	4.9	18.3	37.4	77.2
White, Medium grain	0	1.2	13.2	28.7	44.5
White, Short grain	0	0	4.3	20.0	N/A

N/A = not applicable. All samples above 50 ppb. ppb = µg/kg

5.3.2 AGE-LIMIT SCENARIOS

These scenarios examine the impact, on predicted risk of lifetime cancer, of limiting exposure of infants and children to inorganic arsenic from rice and rice products. For these scenarios, it is assumed that childhood exposure to inorganic arsenic is reduced by either eliminating the consumption of rice and rice products or by consuming products that have lower concentrations. Table 5.7 provides the estimated cancer risk reduction from elimination or reduction in childhood exposure to inorganic arsenic in rice during infancy (< 1 year), and childhood (0 – 6 years). The cancer-risk estimates, expressed as a percentage of the baseline risk (see Section 5.2.1, Table 5.1), and assuming linear relationships, predict 5.6% fewer cancer cases per million when there is no exposure (100% reduction) to inorganic arsenic from rice and rice products during infancy (< 1 year). Eliminating exposure to inorganic arsenic during childhood (0 – 6 years) predicts about a 4-fold risk reduction (23.4%). Reducing exposure, by consuming rice products containing 50% lower concentration of inorganic arsenic (per capita), for example, predicts 2.8% and 11.7% fewer lifetime cases for infant and childhood exposure, respectively.

Table 5.7. Estimated Cancer-Risk Reduction from the Elimination or Reduction of Childhood Exposure to Inorganic Arsenic in Rice and Rice Products

Exposure Reduction	Percentage Reduction of Cancer Risk in Infants (< 1 year)	Percentage Reduction of Cancer Risk in Children (0-6 years)
50%	2.8%	11.7%
100%	5.6%	23.4%

As percentage of predicted total lifetime cancer risk (bladder and lung) attributable to inorganic arsenic in rice and rice products (see Table 5.1).

5.3.3 CONSUMER PRACTICES (RINSING AND COOKING)

Consumer practices, such as rinsing and altering water cooking volume for rice, can affect the level of inorganic arsenic ingested. Several studies report that the total arsenic content of cooked rice is strongly dependent on the cooking protocol and the concentration of arsenic in the water used to prepare the rice (Raab *et al.*, 2009; Sengupta *et al.*, 2006 Signes *et al.*, 2008; Rahman and Hasegawa *et al.*, 2011; Meharg and Zhao, 2012). The available literature provides preliminary estimates that range from 28% to 60% reduction of total and inorganic arsenic from rinsing and cooking practices in water containing low arsenic levels (< 3 µg/L). Because there is substantial uncertainty in these estimates, new research is underway to evaluate not only changes in total and inorganic arsenic levels in rice, but also the impact on nutritional content.

An FDA study measured the effects of rinsing rice and cooking rice in variable amounts of water on inorganic arsenic and nutrients in the cooked grain. Rinsing rice before cooking had a minimal effect on the inorganic arsenic content of the cooked grain but also removed enriched iron, folate, thiamin and niacin. Cooking rice in excess water reduced average inorganic arsenic by 40 to 60% depending on the type of rice and also reduced iron, folate, thiamin and niacin by 50 to 70% in enriched rice (Gray *et al.*, 2016). A brief summary of previous publications is provided below.

Sengupta *et al.* (2006) reported that 57% of the total arsenic was removed from rice native to India (Boro and Aman rice) that contained 203 – 540 µg/kg total arsenic by using a method of multiple washes (five to six times) until the water is clear, then boiling in a 6:1 water:rice ratio. Levels of inorganic arsenic were not provided. About half of the arsenic was lost in the wash water and half in the discard water. A second method, which includes the same rinsing step, although the rice is boiled in water in a 1.5–2:1 ratio of water:rice, also resulted in a reduction of 28% of the total arsenic content. A third method, in which unwashed rice was cooked using a rice:water ratio of 1:1.5–2.0 until no discard water remains, did not modify the arsenic content. The water used in this study contained a small amount of arsenic (< 3 µg/L).

Raab *et al.* (2009) investigated the effect of rinsing, low-volume (2.5:1 water:rice), and high-volume (6:1 water:rice) cooking, and steaming. Several types of rice were investigated, including polished basmati (white), whole-grain basmati (brown), polished long-grain (white), and whole long-grain (brown). Rinsing raw rice with water removed approximately 15% of total arsenic and 5% – 14% of inorganic arsenic, depending on the type of rice. High-volume water: rice cooking effectively removed both total and inorganic arsenic for the rinsed long-grain and basmati rice by an additional 35% and 45% for total and inorganic arsenic content, respectively, compared with uncooked (raw) rice. With both rinsing and cooking with a high volume of water, inorganic arsenic levels were reduced 51%, 54%, and 60% for polished long-grain, whole-grain basmati, and polished basmati, respectively. Although steaming reduced total and inorganic arsenic rice content, it did not do so consistently across all types of rice investigated. Low-water-volume cooking did not remove arsenic. The authors suggest that rinsing is more effective for basmati rice than other types of rice, for reducing total arsenic, and more effective across types of rice, for inorganic arsenic, but that more research is needed. Most of the arsenic lost in washing was inorganic arsenic. This study used double-distilled, deionized water for cooking.

Cooking rice with arsenic-contaminated water can increase arsenic burden. This is of greatest concern in regions of the world with high arsenic groundwater levels, such as Bangladesh and West Bengal, India (Meharg and Zhao, 2012). In a study in which the cooking water contained 40 µg/L (ppb) arsenic, in India, Signes *et al.* (2008) examined two variables on the impact of arsenic concentrations in rice: (1) the cooking method (water volume and inclusion of a washing step); and (2) different processing methods (atab, that is, dry dehusking, and boiled, that is wet dehusking, both in Boro rice variety). Raw atab and boiled rice contained 185 and 315 µg/kg arsenic, respectively. In general, all cooking methods increased total arsenic from the levels in raw rice types. Raw atab rice increased its total arsenic concentrations by 27.6% to 42.2% when cooked in water that contained 40 µg/L arsenic. Raw rice increased total arsenic content by 15.9% or 23.5% when cooked by the intermediate (five-to-six washings and cooked in ratio of 1.5:2 water-to-rice ratio) or contemporary method (unwashed rice cooked in ratio of 1.5:2 water-to-rice ratio), respectively, but decreased its total arsenic by 12.7% when cooked by the traditional method (five-to-six washings followed, by cooking in 6:1 ratio of water to rice). This study demonstrates the impact of arsenic concentration in water on rice levels. Other studies reviewed by Meharg and Zhao (2012) report similar findings. Because the cooking-water levels in these studies exceed the EPA Maximum Contaminant level (MCL) of 10 µg/L for arsenic, these results were not considered further.

As shown previously in Section 4 (Tables 4.3 and 4.5), a comparison of the average inorganic-arsenic concentrations of 58 µg/kg in instant rice versus 96 µg/kg for all rice grain/rice products also demonstrates a reduction of approximately 40%. This value is consistent with and within the range of the literature.

Table 5.8 summarizes the impact of cooking volume on the predicted total lifetime cancer-risk estimates. A 60% reduction for total and inorganic arsenic is provided. Although we provide data for the lifetime and children age groups in Table 5.8, we do not provide data for infants, because of the difficulty in preparing infant cereals using the preparation methods evaluated in this "what if" scenario.

It is important to note that rinsing and cooking in a high volume of water may contribute to a significant loss of vitamins and nutrients in rice, including soluble B vitamins and folate (Gray *et al.*, 2016). Folate, which is part of enriched white rice, is needed for methylation of inorganic arsenic (Lambrou *et al.*, 2012). Low folate and inefficient methylation can be associated with higher toxicities of inorganic arsenic (Gamble *et al.*, 2005).

Table 5.8. Estimated Cancer-Risk Reduction (Median Estimated Total Cancer Cases Per Million per Daily Eating Occasion) for Arsenic in Rice from Changes in Cooking-Water Volume

Age Group	Rice Type	Baseline Cancer Risk Estimates[a]	60% Reduction[b,c] (cooking in 1:6 ratio for rice:water)
Lifetime (0 – 50 years)	White, Long Grain	136	54
Lifetime (0 – 50 years)	Brown[d]	165	66
Children (0 – 6 years)	White, Long Grain	33	13
Children (0 – 6 years)	Brown[c]	26	10

[a] All risk estimates are lifetime. The age range reflects the risk that is attributable to exposure during that interval.
[b] Values presented are the median number of cancer cases per million[c] 60% reduction is the highest reduction reported in Gray et al, unpublished study)
[d] Long-, medium-, and short-grain brown rice

5.3.4 CHANGES IN RICE CONSUMPTION

Consumption frequency and amount consumed per eating occasion of rice and rice products influences the total arsenic intake. As noted previously in Exposure Assessment Section 4, the frequency of consumption varies among different ethnic groups. For example, 32% of the race/ethnicity group identified in NHANES 2003 – 2006 as "Other" (includes Asian and multi-racial populations) consumes rice/rice products one or more times per day, while 17% consumes rice/rice products more than two times per day (see Table 4.7 in Section 4). About 14% of the Mexican-American population consumes rice/rice products three-to-four times per week, while nearly 22% of the White Non-Hispanic population consumes rice/rice products 2-to-3 times per month. To consider this variability and its impact on risk estimates, Table 5.9 provides a range of

risk estimates for different frequency and serving sizes. Baseline predicted lifetime cancer risks are presented in the shaded row, for comparison. As noted previously, the eating-occasion risk estimates assume an individual consumes rice or rice products once per day, 7 days/week, for varying durations, depending on the life stage (i.e., 1 year for an infant, 7 years for a child, and 51 years for an adult).

Table 5.9. Impact of Frequency and Amount Consumed on Predicted Total Lifetime Cancer Risks Attributable to Inorganic Arsenic in Rice and Rice Products (in Median Estimated Total Cancer Cases Per Million)

Rice Consumption Frequency	Infants[a,b] (< 1 year) Rice Cereal, White	Infants[a,b] (< 1 year) Rice Cereal, Brown	Children[a,b] (0 – 6 years)[c] White, Long Grain	Children[a,b] (0 – 6 years)[c] Brown[d]	Lifetime[a,b] (0 – 50 years)[c] White, Long Grain	Lifetime[a,b] (0 – 50 years)[c] Brown[d]
1 serving/day (baseline)	2.8	3.2	33	26	136	162
½ serving/day	1.4	1.6	17	13	68	81
3 servings/week	1.2	1.4	14	11	58	70
2 servings/day	5.6	6.3	66	52	272	330
3 servings/day	8.4	9.5	101	78	408	495

[a] All risk estimates are lifetime. The age range reflects the risk attributable to exposure during that interval.

[b] Values presented are the median number of cancer cases per million

[c] Amounts consumed per eating occasion ("serving") vary by age and rice type. Mean consumption by children (0 – 6 years) is 1.963 g/kg bw/eating occasion for white rice and 1.020 g/kg bw/eating occasion for brown rice; mean lifetime (0 – 50 years) consumption is 1.094 g/kg/eating occasion for white rice and 0.864 g/kg bw/eating occasion for brown rice.

[d] Long, medium-, and short-grain brown rice

6 EXPOSURE AND RISK CHARACTERIZATION OF NON-CANCER HEALTH EFFECTS

This section describes the results of 'what if' scenarios designed to explore the potential impact on non-cancer health effects for pregnant women and infants resulting from changes in exposure including reduced consumption patterns or reduced concentration rates of inorganic arsenic in rice and rice products. FDA will continue to collaborate with EPA to evaluate data for dose-response modeling for these non-cancer health effects.

6.1 PREGNANT WOMEN

In sections 2.6.1,2.6.2, and 9.13 the risk during pregnancy, during infancy and during childhood was characterized based upon the results of a review of the literature and an application of the Bradford Hill criteria for causality. We used the EPA's causal determination framework to categorize the evidence on the different end points into five possible categories: causal relationship, likely to be a causal relationship, suggestive of a causal relationship, inadequate to infer a causal relationship, and not likely to be a causal relationship. For a detailed explanation of the criteria for each category, please see the Causal Framework Table in Appendix 9.14.

EPA's approach and the framework were reviewed by NRC (2013). The NRC supported the five-category approach and recommended that strength-of-evidence judgments be characterized with respect to the modified Bradford Hill criteria for causality. We adopted the same approach as EPA for the assessment of inorganic arsenic in susceptible life stages because it outlined a scientifically defensible approach and assured concordance of methodology between the two federal agencies.

Exposure to inorganic arsenic from drinking water during pregnancy is likely to be causally associated with adverse effects on pregnancy outcomes at low-to-moderate levels of exposure. Pregnant women drink approximately 7% more water, on average, than do non-pregnant women. See Table 6.1.

The results from the NHANES/WWEIA dietary intake survey indicated that approximately 90% of women participants who were pregnant at the time of the survey reported consuming rice grain or rice products at least once during a 2-day period. Below are the results of the NHANES survey (Tables 6.2 – 6.4).

Although there are limited data, it appears that pregnant women consume slightly higher levels of inorganic arsenic from the combination of drinking water, rice grain, and rice products, compared with non-pregnant women. Reducing consumption of rice grain would decrease a

woman's daily exposure to inorganic arsenic by approximately 5.2 – 7.8 µg/serving or 75 – 119 ng/kg bw/serving.

Table 6.1. Drinking Water Intake by Pregnant Women and by Non-Pregnant Women, 16 – 49 years of age

Population	Total N[a]	N eaters[a]	% eaters	Mean Drinking Water Intake[b] (Consumers Only) mL/day	90th Percentile Drinking Water Intake[b] (Consumers Only) mL/day	Mean Drinking Water Intake[b] (Consumers Only) mL/kg bw/day	90th Percentile Drinking Water Intake[b] (Consumers Only) mL/kg bw/day
Pregnant women	664	620	91.7	1297	2535	17.5	34.0
Non-pregnant women	5723	5041	89.0	1151	2350	16.2	33.8

[a] unweighted

[b] Data source for drinking water intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Analyses conducted using FARE v. 10.05. Intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert her intake from mL/day to intake in mL/kg bw/day.

Table 6.2. Daily Consumption of Rice Grain and Rice Products by Pregnant Women and Non-Pregnant Women, 16 – 49 years of age

Population	Rice Type	Total n[a]	n eaters[a]	% eaters	2-day average[b] g/kg bw/day per capita	2-day average[b] g/kg bw/day per consumer
Pregnant women	All	672	611	89.8	0.223	0.249
Pregnant women	Brown	672	55	12.3	0.032	0.262
Pregnant women	White	672	603	87.5	0.191	0.218
Non-pregnant women	All	5727	4997	87.2	0.206	0.237
Non-pregnant women	Brown	5727	423	8.9	0.017	0.195
Non-pregnant women	White	5727	4934	86.0	0.189	0.220

[a] unweighted

[b] Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.1. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert her intake in g/day to intake in g/kg bw/day.

Table 6.3. Consumption of Rice as Cooked Regular or Instant Rice, per Eating Occasion, by Pregnant Women and Non-Pregnant Women, 16 – 49 years of age

Population	Rice Type	Total n[a]	n eaters[a]	% eaters	Rice Intake Per Eating Occasion[b] g/eating occasion	Rice Intake Per Eating Occasion[b] g/kg bw/eating occasion
Pregnant women	Brown	672	17	4.5	50.5	0.777
Pregnant women	White	672	101	15.7	56.5	0.809
Non-pregnant women	Brown	5727	125	2.3	49.7	0.782
Non-pregnant women	White	5727	782	12.7	49.6	0.770

[a] unweighted

[b] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert her intake in g/eating occasion to intake in g/kg bw/eating occasion.

Table 6.4. Exposure to Inorganic Arsenic from Cooked Regular or Instant Rice, per Eating Occasion, by Pregnant and Non-Pregnant Women of Childbearing Age

Population	Rice Type	Total n[a]	n eaters[a]	% eaters	iAs in rice[b] (ppb)	Exposure to Inorganic Arsenic from Rice[c] µg/eating occasion[d]	Exposure to Inorganic Arsenic from Rice[c] ng/kg bw/eating occasion[e]
Pregnant women	Brown	664	17	4.5	153.7	7.8	119.4
Pregnant women	White	664	101	15.7	92.3	5.2	74.7
Non-pregnant women	Brown	5727	125	2.3	153.7	7.6	120.2
Non-pregnant women	White	5727	782	12.7	92.3	4.6	71.1

[a] unweighted

[b] Data sources for inorganic arsenic (iAs) concentration: FDA (2013) and Consumer Reports (2012); ppb = ng iAs/g rice or µg iAs/kg rice

[c] Data source for rice intake data: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. The body weight of each NHANES respondent was used to convert her intake in µg/eating occasion to intake in ng/kg bw/eating occasion.

[d] Calculated as: (ng iAs/g rice) * g rice/eating occasion = µg iAs/eating occasion.
[e] Calculated as: (ng iAs/g rice) * g rice/kg bw/eating occasion = ng iAs/kg bw/eating occasion.

6.2 "WHAT IF" EXPOSURE SCENARIOS FOR INFANTS

Compared with adults, young children (< 4 years of age) are more sensitive to the adverse health effects of inorganic arsenic. Additionally, young children (< 4 years of age) have intakes of food two- to three-fold higher, on a per body weight basis, compared with adults (EFSA, 2009). Therefore, a child's daily exposure to contaminants in food, such as inorganic arsenic in rice, could potentially be much higher than that of adults. Exposure to inorganic arsenic in early childhood is likely associated with neurotoxic effects, particularly in IQ test results in children.

The following three "what if" scenarios were conducted to evaluate the potential impact of reducing exposure of infants to inorganic arsenic from infant rice cereal:

1) Impact of establishing mandatory or voluntary inorganic arsenic limits for infant rice cereals

2) Impact of change in frequency of consumption of infant rice cereals

3) Impact of lowering the levels of inorganic arsenic in infant cereals, combined with reducing consumption

6.3 MANDATORY OR VOLUNTARY LIMITS FOR RICE INTENDED FOR BABY FOODS

FDA's and Consumer Reports' combined sampling of marketed infant white-rice cereals found that an average level of inorganic arsenic in this product was 103.9 µg/kg. We estimated per capita inorganic arsenic exposures by month during the first year of life using the methodology described in section 4.3.1. The following chart demonstrates the reduction in per capita exposure to inorganic arsenic for children from 1 – 12 months of age, if the rice used in the production of infant cereal had lower levels of inorganic arsenic. For example, using rice that has only about half (50 µg/kg) the level of inorganic arsenic results in almost a 50% decrease in exposure to inorganic arsenic. This is especially critical at the times of peak consumption of infant cereal, at 5 – 7 months of age.

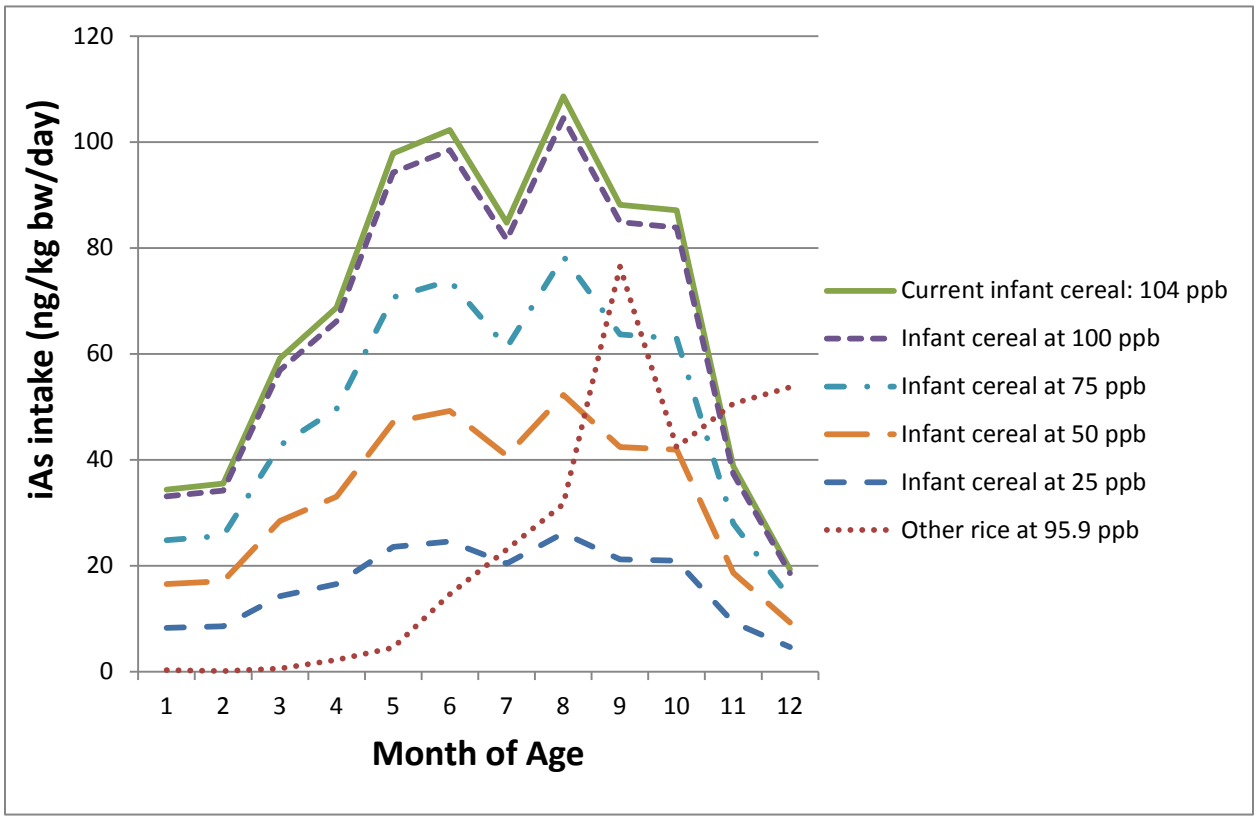

Figure 6.1. Inorganic Arsenic (iAs) Intake from White-Rice Cereal and Regular Rice at Current and Hypothetical Inorganic Arsenic Levels by Infants 0 – 12 Months of Age

Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. Mean per capita inorganic arsenic exposures were estimated using the methodology described in section 4.3.1. N at each month of age ranged from 119 to 145. The number of infant cereal consumers ranged from 10 during the first month of life to 81 at 5 months of age.

6.4 CHANGES IN INFANT RICE CEREAL CONSUMPTION

The second scenario looks at the effect of reducing consumption of infant cereal during the first year of life. In a hypothetical scenario, we calculate that consumption of three average sized servings a day of infant white-rice cereal, at its current inorganic arsenic concentration of 103.9 µg/kg, would result in the infant being exposed to between about 0.3 – 0.5 µg/kg bw/day (0.03 – 0.3 µg/kg bw/day on the per capita basis) of inorganic arsenic depending on the month of age. Reduction of consumption to 1 serving per day reduces the risk by about two-thirds, but it still is in the range of 0.1 – 0.15 µg/kg bw/day (0.01 – 0.1 µg/kg bw/day on the per capita basis). Reducing consumption of infant cereal to two servings per week would have the most dramatic

effect. Exposure would drop to below about 54 ng/kg bw/day (below 26 ng/kg bw/day on the per capita basis), averaged over the week.

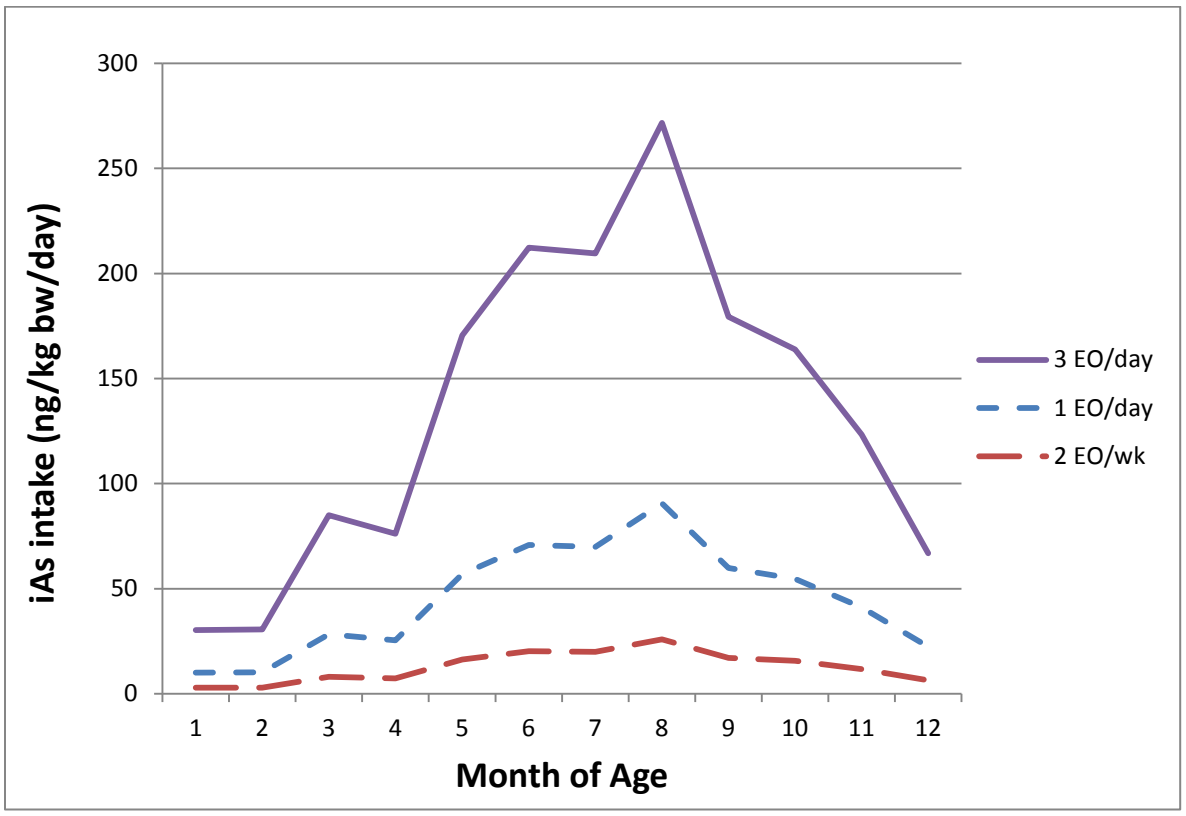

Figure 6.2. Hypothetical Variation in Daily Inorganic Arsenic (iAs) Intake from Infant White Rice Cereal, Based on Number of Cereal-Eating Occasions (EO)

Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. 1,000 nanograms = 1 microgram

N at each month of age ranged from 119 to 145. The number of infant cereal consumers ranged from 10 during the first month of life to 81 at 5 months of age.

6.5 MANDATORY OR VOLUNTARY LIMITS PLUS CHANGES IN INFANT RICE-CEREAL CONSUMPTION

The third hypothetical scenario demonstrates the effect of lowering the level of inorganic arsenic in infant cereals combined with reducing the consumption of infant cereal to either one average sized serving a day or to two servings per week. Other combinations are possible. This information is provided as an example to illustrate the impact of both inorganic arsenic limits

and reduced consumption. Reducing both the level of inorganic arsenic in infant cereals combined with reducing consumption of rice cereal to two times per week could, potentially, reduce exposure to inorganic arsenic from intakes as high as 153 ng/kg bw/day (91 ng/kg bw/day on the per capita basis) to intakes of 32 ng/kg bw/day or less (19 ng/kg bw/day or less on the percapita basis), averaged over the week.

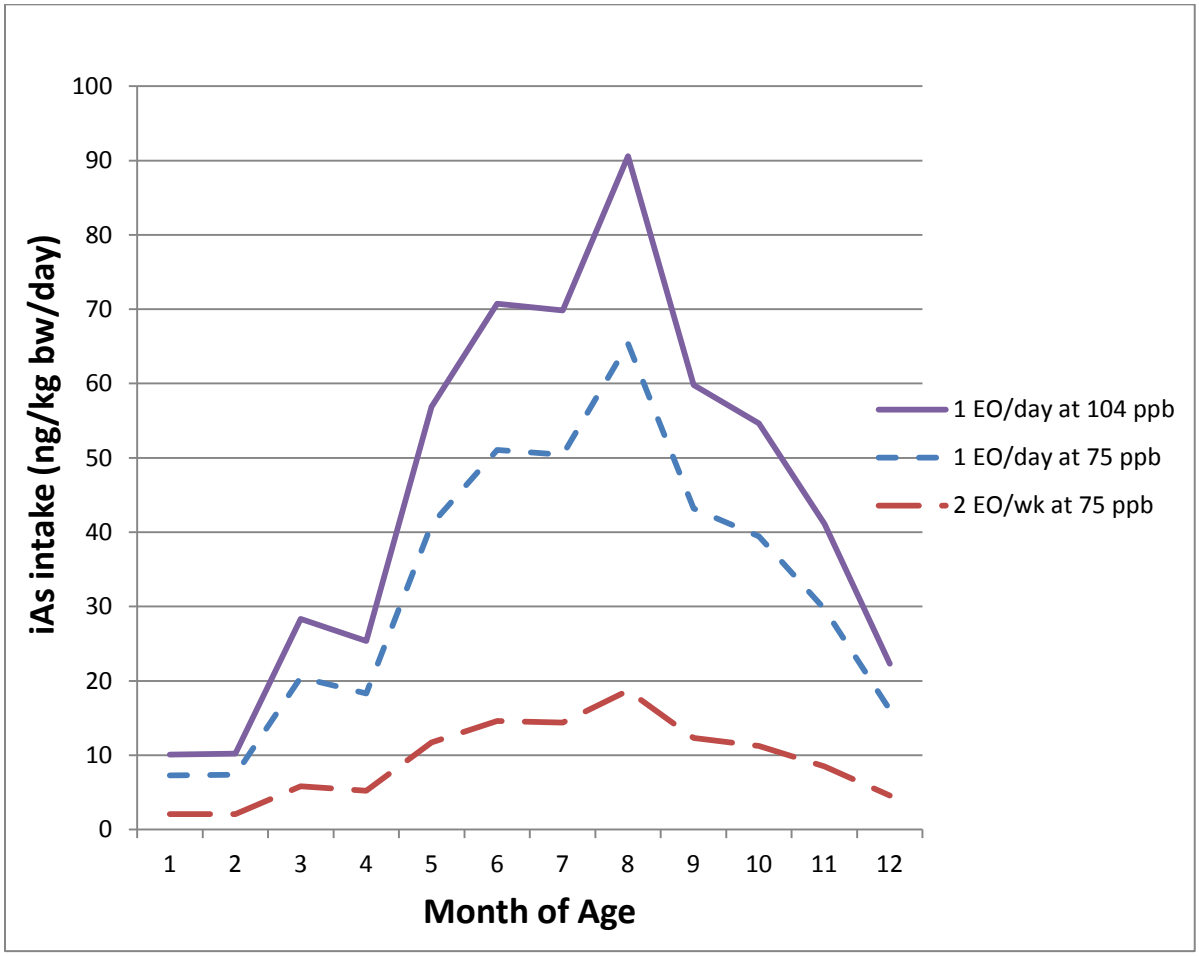

Figure 6.3. Hypothetical Variation in Daily Inorganic Arsenic (iAs) Intake from Infant White-Rice Cereal, Based on the iAs Concentration and Number of Cereal-Eating Occasions (EO)

Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates. 1,000 nanograms = 1 microgram

N at each month of age ranged from 119 to 145. The number of infant cereal consumers ranged from 10 during the first month of life to 81 at 5 months of age.

7 CONCLUSIONS

This risk assessment included an analysis of the available scientific information and data, to (1) quantitatively predict cancer effects from exposure to inorganic arsenic from consumption of rice grain and rice products and (2) qualitatively evaluate certain non-cancer effects. Predicted number of cancer cases per million and its 90% confidence interval are provided for different food-intake levels, exposure at different life stages, and different types of rice.

7.1 ANSWERS TO THE RISK ASSESSMENT QUESTIONS

1) Which foods or food products contribute the most to arsenic exposure from the diet?

There are two forms of arsenic in food, inorganic and organic. Most studies conducted over the last several decades have analyzed foods for total arsenic alone, and few studies or surveys have focused on exposure to speciated arsenic. FDA's Total Diet Study (TDS) measures only total arsenic. Among the top 25 foods from TDS: (1) the highest levels of total arsenic were in seafood (mean 5.5 mg/kg from 1991 to 2011, haddock); (2) eight of the top 25 foods were rice grain or rice products; and (3) other foods included raw mushrooms, fried chicken products, and peanut butter (Appendix 9.1). However, because organic forms of arsenic are far less toxic and comprise the major form of arsenic in seafood, total arsenic determinations are not useful for comparing the risk from various food sources.

This risk assessment addresses a major contributor to the dietary burden of inorganic arsenic: rice grain and rice products. FDA's sampling indicated that rice has the highest levels of inorganic arsenic, compared with other sampled food commodities, and rice is an ingredient of many products that consumers routinely eat. To estimate the total dietary burden from exposure from all foods consumed, additional data are needed, including information on the levels of inorganic arsenic in other foods.

2) What are the adverse health effects from exposure to different forms of arsenic (inorganic vs. organic) in rice?

NRC (2013) considered a variety of cancer and non-cancer adverse health effects associated with exposure to inorganic arsenic. These health effects (cancer, adverse pregnancy outcomes, and neurodevelopmental effects) and the level of evidence linking each to exposure to inorganic arsenic are discussed in this report.

FDA acknowledges that, in addition to cancer, inorganic arsenic has been associated with many non-cancer effects, including ischemic heart disease, diabetes, skin lesions, renal disease, hypertension, and stroke. Assessing all the risks associated with inorganic arsenic would take considerable time and resources and would delay taking any needed action to protect public health. Therefore, for this risk assessment, FDA looked at cancer effects (lung and bladder cancer) for the general population and certain non-cancer effects for susceptible life stages: pregnancy, infancy, and early childhood. Additionally, we plan to continue to work with our federal partners, including EPA, NIEHS, CDC, and USDA, as new data emerge on the adverse health endpoints associated with inorganic arsenic and on mitigation strategies for lowering levels of inorganic arsenic in food.

3) Are pregnancy, infancy, and/or early childhood periods of greater susceptibility to non-cancer effects of oral exposure to inorganic arsenic, and if so, can these risks be quantified?

There is evidence that pregnancy, infancy, and early childhood are periods of greater susceptibility to the adverse effects of oral exposure to inorganic arsenic. See Appendix 9.15 for detailed study data. There is also emerging evidence that inorganic arsenic exposure during early childhood can have neurotoxic effects (for example, changes in IQ). Whether these effects are temporary or permanent has yet to be understood.

Susceptibility to the toxic effects of inorganic arsenic during pregnancy and infancy/early childhood is an area of active research, and it may be possible to quantify these risks in the near future. Daily exposure to inorganic arsenic would be lowered by reducing the frequency of consumption, or, for infant cereal, by reducing the level of inorganic arsenic in the product, or both.

4) What are the predicted risks of cancer from long-term exposure to inorganic arsenic from consuming rice grain and rice products, for the total U.S. population, and what is the risk attributable to exposure only during infancy and childhood?

The model predicts 39 cases per million (median estimated lifetime risk of lung and bladder cancer) from consumption of all rice grain and rice products. FDA calculated that this is a small portion of an estimated 90,000 cases per million of lung and bladder cancer cases in the U.S. (6.6% lifetime risk for lung cancer and 2.4% lifetime risk for bladder cancer). Predicted cancer risk is 2.3 cases per million for exposure only during infancy (up to 1 year old), and 9.1 cases per million for exposure during childhood (up through 6 years old) alone. Assuming a U.S. population of 317 million and an average life expectancy of 78.6 years, we estimate for the U.S. population 154 annual lung and bladder cancers associated with dietary inorganic arsenic. The confidence interval for this estimate is 0 to 314 annual cases.

5) What is the predicted lifetime risk of cancer from exposure to inorganic arsenic from rice grain and rice products, expressed on the basis of the population (i.e., cases per million) and the individual (i.e., cases per serving)?

To estimate the risk to the population, the per capita consumption estimates were used (see Table 5.1). To characterize the risk to an individual, we estimated the risk assuming one eating occasion (serving) per day for the duration of exposure (see Table 5.2).

The lifetime risk (cases per million) for different exposure periods and exposure estimates (per capita, per serving) are summarized below:

Table 7.1. Lifetime Risk for Different Exposure Periods and Exposure Estimates

Exposure Period	Exposure Estimate	Food Products	Cancer Risk (cases/million) (CI90%)
Infancy (< 1 yr)	Average per capita	All rice and rice products incl infant rice cereal	2.3 (0, 4.6)
Childhood (0 – 6 yrs)	Average per capita	All rice and rice products	9.1 (0, 19)
Lifetime (0 – 50 yrs)	Average per capita	All rice and rice products	39 (0, 79)
Infancy (< 1 yr)	Per daily serving	Infant cereal (white rice)	2.8(0, 5.7)
Childhood (0 – 6 yrs)	Per daily serving	White long grain rice	33 (0, 67)
Lifetime (0 – 50 yrs)	Per daily serving	White long grain rice	136 (0, 278)

6) Are there differences in the predicted risk from the consumption of different types of rice grain (e.g., white rice, brown rice)?

There are differences in the predicted risk associated with different types of rice grain. The predicted risk is a function of consumption and levels of inorganic arsenic in these products. For example, the predicted lifetime cancer risk is 34 cases/million for white rice, compared with 5.4 cases/million for brown rice. Although the concentration of inorganic arsenic is generally higher in brown, compared with white, rice grain, the higher risk associated with white rice is primarily a function of the higher consumption of this product. There are also differences in predicted risk among the different types of white and brown rice per serving. For example, the predicted

lifetime cancer risk from consuming one serving per day of white basmati rice is 82 cases per million, while the predicted cancer risk from consuming one serving per day of brown basmati rice is 139 cases per million.

7) What is the impact, on the predicted risk of cancer, of mitigations or interventions that reduce dietary exposure to inorganic arsenic from rice grain and rice products?

Mitigations that reduce the levels of inorganic arsenic in the product, reduce the frequency of consumption, or reduce the amount consumed per eating occasion will proportionally reduce the risk. Setting a limit below 150 ppb inorganic arsenic in rice grain and rice products would decrease the risk and lower the limit. The reduction in estimated risk and corresponding loss of product from the marketplace (i.e., percentage of rice grain estimated to be above the limit, based on available testing data), would be as follows:

Table 7.2. Inorganic Arsenic Limits, the Range of Risk Reduction and the Associated Loss of Rice in the Food Supply at that Limit

Limit on inorganic arsenic (ppb)	Range of risk reduction, depending on product	Range of loss of rice in the food supply
150	0% – 23%	0% – 56%
100	2% – 47%	4% – 93%
75	17% – 79%	14% – 99%

7.2 UNCERTAINTY AND LIMITATIONS OF THE CANCER RISK ASSESSMENT

As with any risk assessment, we acknowledged and described, where possible, uncertainty about the risk estimate; for example, regarding data availability and quality. This FDA risk-assessment model for cancer endpoints used a Monte-Carlo uncertainty analysis to represent these uncertainties quantitatively, where possible. The major source of uncertainty in this FDA model is in the dose-response relationship. The model quantifies, in a comprehensive manner, the uncertainty arising from the original epidemiological studies (dose estimation, statistical sampling error) and the selection of dose-response models. Considering these sources of uncertainty leads to larger confidence intervals of the estimated risk for a given dose (see Figures 3.2 and 3.3). For comparison, we also employ a linear model previously used by the EPA (Morales *et al.*, 2000; EPA, 2001), from a different data set, which has a confidence interval that reflects sampling error, but does not reflect uncertainty in the dose estimates or model uncertainty.

The model we developed for our risk assessment suggests a linearity of the dose-response in the range of the exposure considered for the U.S. diet (see Table 3.6). Our model (and the previous FDA-developed model, regarding arsenic in apple juice, Carrington *et al.*, 2013) does not use a linear extrapolation from a benchmark dose (BMD), as suggested by the current EPA (2005) cancer risk assessment guidelines. The FDA model is consistent with the NRC suggestion to fit linear or non-linear models to observed data (NRC, 2013, Box 7). Although NRC provided an example that used a single dose-response model form, eight alternative models were considered for the FDA dose-response derivation, and these eight were used to represent model uncertainty. The eight alternative models used to characterize the shape of the dose-response relationship were employed to estimate the risk below the range of statistically significant differences among groups, as was recommended by NRC (2013).

None of the alternative models evaluated by FDA is linear at high doses (7.5 µg/kg bw), which is approximately equivalent to 100 µg/L in water), but each of them is approximately linear at low doses. Sensitivity analysis also provided insight to any limitations in interpreting and using the data. The impact of model form on the estimate is explored in Appendix 9.4.

Comparatively, the uncertainty associated with the FDA exposure-assessment model, including the mean level of contamination of rice and rice products or the uncertainty about the consumption level, has a lower impact on the uncertainty of risk estimates, when compared with the uncertainty associated with the dose-response relationship. Uncertainties in the exposure assessment include limitations of both the sampling and consumption data, including:

1) a small number of samples analyzed for some product types (notably brown parboiled and brown instant rice);

2) use of sampling data not statistically designed to reflect availability of different products across the U.S.;

3) assumption that inorganic arsenic concentrations in rice grain are representative of inorganic arsenic concentrations in processed rice products, such as rice crackers, rice cakes, and rice beverage;

4) potential intake of rice by adults may be overestimated, due to EPA's assumption that all beer contains rice as an ingredient; and

5) estimation of intakes of specific types of rice (e.g., jasmine rice, basmati rice) using market-share data, because the NHANES/WWEIA data did not distinguish between different types of rice.

Further sensitivity of the model to changing data inputs can be observed from the "what if" scenarios conducted. Because the risk estimates are approximately linear over the range of dietary exposure in the United States, many of the tested scenarios presume that the risk is directly proportional to exposure.

7.3 POTENTIAL FUTURE RESEARCH AND RISK-ASSESSMENT ACTIVITIES

In the development of this risk assessment, we identified research and risk assessment activities that would assist in refining and reducing uncertainty in the model estimates, including the following:

- new surveys on representative data samples, including speciation of arsenic in commonly consumed foods;
- meta-analyses of epidemiological studies, or other scientific information to help determine the amount of dietary arsenic linked to health effects, including those not assessed in the current risk assessment, such as cardiovascular effects and diabetes;
- early-life exposure to arsenic, using models that include timing and amount of exposure as variables;
- adverse health effects of inorganic arsenic in certain susceptible life stages;
- improved methods for characterization of exposure from epidemiological data for dose-response; and
- agricultural and processing practices that would reduce arsenic content of rice.

7.4 KEY FINDINGS

1) Arsenic, a contaminant found in the environment naturally or as a result of human activity, is present in a variety of foods. For many of these products, insufficient data are available to evaluate the amount of total arsenic and/or the proportion that is inorganic vs. organic. Inorganic forms are the primary toxic forms of arsenic. See section 2.1 for more information.

2) Sampling surveys provided the levels of inorganic arsenic in rice and rice products. The estimated mean inorganic arsenic concentration was 92 ppb in white rice and 154 ppb in brown rice. The mean inorganic arsenic concentration in dry infant brown-rice cereal was 119 ppb, and the mean inorganic arsenic concentration in dry infant white-rice cereal was 104 ppb. These levels do not pose a health concern for immediate toxicity, but the levels may pose a risk following long-term exposure. See section 4.2 for more information.

3) Two organic arsenic species, MMA and DMA, were also measured in rice and rice products. The main species found was DMA. We estimated the exposure to DMA using the mean concentration in infant rice cereal (77 ppb) and the highest mean concentration in rice grain and rice products (131 ppb). See section 4.7 for more information.

4) The predicted cancer risk (lung and bladder) for the U.S. population is estimated to be 39 (90% CI: 0, 79) cases per million for lifetime exposure (per capita) for all rice grain and rice products. This is a small portion of an estimated 90,000 cases per million of lung and bladder cancer cases in the U.S. (6.6% lifetime risk for lung cancer and 2.4% lifetime risk for bladder cancer). The majority of the total risk is attributed to white rice, due to the higher consumption of this product, compared with consumption of brown rice. The predicted risk for one average serving per day over a lifetime varies according to the rice product, from 74 (0, 157) to 184 (0, 444) cases per million. More servings per day would increase the risk almost proportionally. See sections 2.5 and 5.2 for more information.

5) Reducing exposure to inorganic arsenic from rice grain and rice products reduces lifetime risk of cancer. Eliminating rice grain and rice products from the diet during infancy (< 1 year) and childhood (0 – 6 years) would potentially reduce the lifetime risk of cancer for the U.S. population from exposure to inorganic arsenic in rice and rice products by approximately 6% and 23%, respectively. This dietary change would also potentially reduce the risk of non-cancer adverse health effects. See section 5.3 for more information.

6) Mandatory or voluntary limits on inorganic arsenic in rice grain and rice products above 200 ppb were not predicted to significantly change the predicted risk for the U.S. population, except for brown rice (4-11% reduction). A mandatory or voluntary limit of 150 ppb reduces the predicted cancer risk between 0 and 23%; and a mandatory or voluntary limit of 100 ppb reduces predicted cancer risk between approximately 2% and 47%, depending on the type of rice. A mandatory or voluntary limit of 75 ppb would reduce predicted cancer risk approximately between 17% and 79%. See section 5.3 for more information.

7) Reducing the concentration of inorganic arsenic in infant rice cereal to 75 ppb from 104 ppb and reducing consumption to 2 average servings per week from 3 servings per day would reduce exposure to inorganic arsenic from infant rice cereal from a peak of about 460 ng/kg bw/day to 32 ng/kg bw/day. See section 6.5 for more information.

8) Data indicate that rinsing/cooking practices have variable impact on reducing arsenic levels in rice. However, these practices also reduce enriched iron, folate, thiamin and niacin.See section 5.3 for more information.

9) Decreasing the amount consumed per eating occasion and frequency of consumption could reduce cancer risk proportionally. Decreasing frequency from 1 serving of long grain white rice per day to 1/2 serving per day would result in a predicted reduction of the lifetime risk from 136 to 68 cases per million. See section 5.3 for more information.

This risk assessment significantly advances our ability to describe the current state of knowledge about arsenic in rice and rice products, while simultaneously providing a framework for integrating, evaluating, and applying new scientific knowledge for public-health. The scientific evaluations and mathematical model provide a systematic assessment of the scientific knowledge needed to review effectiveness of current policies, programs, and practices and identify new strategies for minimizing the public-health impact of arsenic in rice and rice products. This risk assessment builds on previous research and collaborations by FDA and other agencies. As an important part of the process, and in the interest of transparency, the report will now undergo public comment and the risk assessment and report may be revised accordingly. We will also continue to work with our federal partners, as new research emerges on the risks of inorganic arsenic to consumers.

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9 APPENDIX

9.1 TOTAL ARSENIC IN SELECT FOODS FROM THE TOTAL DIET STUDY

Table 9.1. Total Diet Study: Highest % Detects of Total Arsenic, Top 25 Foods, 1991-2011

Food Description	# Samples	# Non-Detects	# Detects	% Detects	Mean (ND=0) (mg/kg)	Min	Max
Haddock	19	0	19	100%	5.5376	0	10.43
Fish sticks or patty, frozen, oven-cooked	75	0	75	100%	0.6780	0	2.792
Tuna, canned in water, drained	36	0	36	100%	1.0108	0	1.875
Fried rice, meatless, from Chinese carry-out	36	0	36	100%	0.0677	0	0.106
BF, cereal, rice, dry, prepared w/ water	36	0	36	100%	0.0441	0	0.066
BF, cereal, rice w/apples, dry, prepared w/ water	25	0	25	100%	0.0336	0	0.052
Shrimp, boiled	74	1	73	99%	0.5637	0	2.681
Tuna, canned in oil, drained	39	1	38	97%	0.9286	0	1.71
Clam chowder, New England, canned, cond, prepared w/ whole milk	75	2	73	97%	0.1384	0	0.279
Mushrooms, raw	75	2	73	97%	0.0733	0	0.203
Granola bar, w/ raisins	36	1	35	97%	0.0324	0	0.058
Salmon, steaks/fillets, baked	55	2	53	96%	0.3972	0	1.193
Fish sandwich on bun, fast-food	75	3	72	96%	0.4815	0	1.6
Crisped rice cereal	75	3	72	96%	0.1464	0	0.505
Tuna noodle casserole, homemade	75	3	72	96%	0.1240	0	0.321
Rice, white, enriched, cooked	75	3	72	96%	0.0694	0	0.128
Granola w/ raisins	75	8	67	89%	0.0206	0	0.061
Chicken leg, fried, fast-food (w/ skin)	36	4	32	89%	0.0183	0	0.044
Chicken breast, fried, fast-food (w/ skin)	36	4	32	89%	0.0170	0	0.037
Oat ring cereal	75	13	62	83%	0.0226	0	0.054
BF, cereal, rice, instant, prepared with whole milk	39	7	32	82%	0.0423	0	0.087
Chicken, fried (breast, leg, and thigh), fast-food	39	7	32	82%	0.0243	0	0.083
Green peppers stuffed with beef and rice, homemade	39	7	32	82%	0.0172	0	0.06
BF, cereal, rice w/apples	17	4	13	76%	0.0105	0	0.02
Chicken, drumsticks and breasts, breaded and fried, homemade	39	12	27	69%	0.0196	0	0.086

Note: ND = non-detects

Table 9.2. Total Diet Study: Highest Mean of Total Arsenic (mg/kg), Top 25, 1991-2011

Food Description	# Samples	# Non-Detects	# Detects	% Detects	Mean (ND=0) (mg/kg)	Min	Max
Haddock	19	0	19	100%	5.5376	0	10.43
Tuna, canned in water, drained	36	0	36	100%	1.0108	0	1.875
Tuna, canned in oil, drained	39	1	38	97%	0.9286	0	1.71
Fish sticks or patty, frozen, oven-cooked	75	0	75	100%	0.6780	0	2.792
Shrimp, boiled	74	1	73	99%	0.5637	0	2.681
Fish sandwich on bun, fast-food	75	3	72	96%	0.4815	0	1.6
Salmon, steaks/fillets, baked	55	2	53	96%	0.3972	0	1.193
Crisped rice cereal	75	3	72	96%	0.1464	0	0.505
Clam chowder, New England, canned, cond, prepared w/ whole milk	75	2	73	97%	0.1384	0	0.279
Tuna noodle casserole, homemade	75	3	72	96%	0.1240	0	0.321
Mushrooms, raw	75	2	73	97%	0.0733	0	0.203
Rice, white, enriched, cooked	75	3	72	96%	0.0694	0	0.128
Fried rice, meatless, from Chinese carry-out	36	0	36	100%	0.0677	0	0.106
BF, cereal, rice, dry, prepared w/ water	36	0	36	100%	0.0441	0	0.066
BF, cereal, rice, instant, prepared with whole milk	39	7	32	82%	0.0423	0	0.087
BF, cereal, rice w/apples, dry, prepared w/ water	25	0	25	100%	0.0336	0	0.052
Granola bar, w/ raisins	36	1	35	97%	0.0324	0	0.058
Chicken, fried (breast, leg, and thigh), fast-food	39	7	32	82%	0.0243	0	0.083
Oat ring cereal	75	13	62	83%	0.0226	0	0.054
Granola w/ raisins	75	8	67	89%	0.0206	0	0.061
Chicken, drumsticks and breasts, breaded and fried, homemade	39	12	27	69%	0.0196	0	0.086
Chicken leg, fried, fast-food (w/ skin)	36	4	32	89%	0.0183	0	0.044
Green peppers stuffed with beef and rice, homemade	39	7	32	82%	0.0172	0	0.06
Chicken breast, fried, fast-food (w/ skin)	36	4	32	89%	0.0170	0	0.037
Peanut butter, creamy	75	44	31	41%	0.0126	0	0.086

Note: ND = non-detects

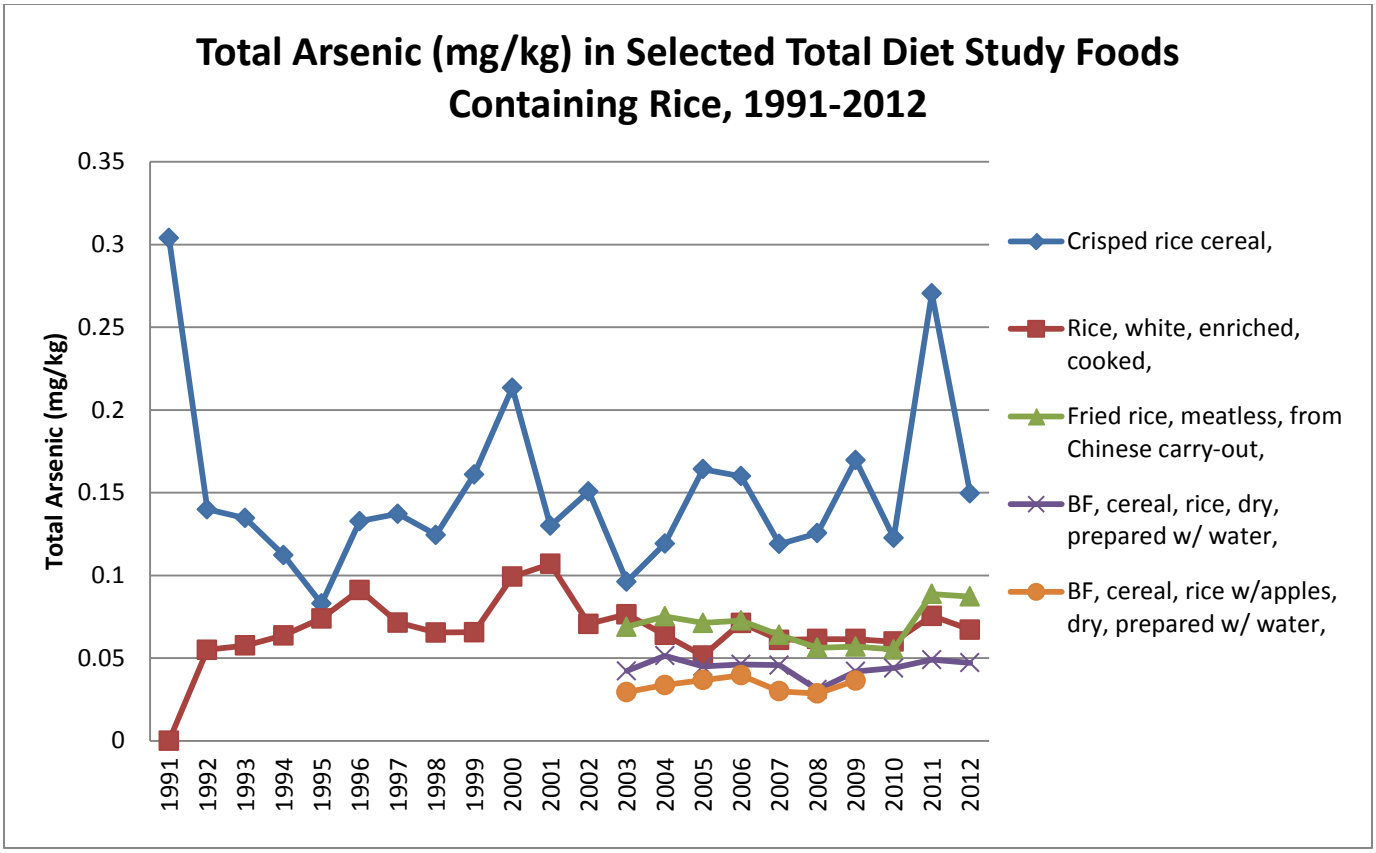


Figure 9.1. Total Arsenic in Selected Total Diet Study Foods Containing Rice, 1991-2012

9.2 ADJUSTMENT OF THE DOSE-RESPONSE MODELS TO THE BOOTSTRAP SETS

9.2.1 MAXIMUM LIKELIHOOD PROCEDURE

For each of the N_u = 1,000 bootstrap sets, eight dose response models for dichotomous data were fitted independently: the gamma model, the logistic model, the log-logistic model, the log-probit model, the probit model, the Weibull model, the one-stage model and the dichotomous Hill model.

Appendix 9.3 describes the 8 models and their parameterization in PROAST (version 32.2, Dutch National Institute for Public Health) and BMDS version 2.4.0 (EPA, 2013c). The models (with the exception of the logistic, the probit and the one-stage models) were used in their restricted form. This typically keeps the estimated models from assuming biologically unrealistic patterns (e.g., such as infinite slopes for very low doses or non-monotonicity). In addition, for all models, responses and doses are restricted to be > 0; $\beta \geq 0$), and the background incidence parameter is restricted to be greater than zero.

Parameters were estimated using maximum likelihood methods, as implemented in PROAST and BMDS. For the k doses d_i, i={1,…,k}, if n_i individuals respond among N_i individuals, the distribution of n_i is assumed to be binomial with probability $p_i = f(d_i, \boldsymbol{\theta})$, where f is the dose-response model with parameters $\boldsymbol{\theta}$ evaluated at d_i. The log-likelihood function L is $L = \sum_{i=1}^{k} L_i(N_i, n_i, d_i; \boldsymbol{\theta})$, where $L_i = n_i \ln(p_i) + (N_i - n_i)\ln(1 - p_i)$. The maximum likelihood estimator (MLE) is the vector $\boldsymbol{\theta}$ that maximizes the likelihood function within the domain of definition of $\boldsymbol{\theta}$.

$\boldsymbol{\theta}$ is estimated using a constrained optimization routine. These routines starts from a set of initial parameters and local maxima could be obtained. To avoid this, for each (model - bootstrap sample) pair, the parameters were estimated from multiple starting points:

- one set of initial parameters as estimated using the routines used in BMDS (gamma and dichotomous Hill model) or the routine used in PROAST (other models), and;

- a grid of (10 × 10) (for 2-parameter models) or (5 × 5 × 5) (for 3-parameter models) values. The grid was built using an equally spaced set of values for each parameter over a reasonable range of values for that parameter.

As an example, the MLE for the gamma model was estimated by running the maximization procedure 126 times per sets, i.e. once at the initial parameters as estimated by the BMDS routine and 125 times using a grid built from 5 values for a (from 0 to the maximum prevalence

obtained over all bootstrap samples at the lowest dose), 5 values for *b* (from 0.1 to 5) and 5 values for *c* (from 1 to 18).

The general MLE was the vector of parameters that led to the maximum likelihood over all these maximization procedures.

9.2.2 IMPLEMENTATION

PROAST works under R (© The R Core Team). Its code is open.

A specific R code was developed to automate the fit of the 8 models to the 1,000 bootstrap samples, using the 101 – 126 initial sets of parameter. This R code uses the PROAST major function for ML estimation ("f.nlminb" function) and the PROAST routines used to evaluate a set of initial parameters (adapted from the "f.start.bin" function, all model, but gamma model). The procedure to evaluate the ML estimates for the dichotomous Hill model was specifically written in R as it is not part of the PROAST (v.32.2) distribution.

The functions that evaluate the set of initial parameters for the gamma and the dichotomous Hill model were translated in R from the C code provided by EPA with the BMDS distribution.

9.3 MODELS

The description of the models as parameterized in PROAST (v.32.2) was extracted from the actual R code. The description of the models as parameterized in BMDS was extracted from the respective manual (EPA, 2013d). In all cases, the models were employed to estimate extra risk where the incremental increase in disease frequency above background rates is estimated. In addition to the restrictions noted for individual models, background incidence parameters were restricted to be greater than zero.

9.3.1 RESTRICTED DICHOTOMOUS GAMMA MODEL

PROAST: Prob{response} = a + (1-a) pgamma(b × dose; c), with $0 \leq a \leq 1$, $b \geq 0$ and $c \geq 1$ in the restricted version, where pgamma(s, r) is the distribution function for the gamma distribution with shape parameter s and rate parameter r.

BMDS: Prob{response} = γ + (1-γ) G(α; β dose), with $0 \leq \gamma \leq 1$, $\beta \geq 0$ and $\alpha \geq 1$ in the restricted version, where G(s; x) is the incomplete gamma integral $G(s,x) = \frac{1}{\Gamma(s)} \int_0^x t^{s-1} e^{-t} dt$.

Correspondance (from BMDS to PROAST) in parameters: $\alpha = c$; $\beta = b$ and $\gamma = a$.

Starting values: as implemented in BMDS

9.3.2 LOGISTIC MODEL

PROAST: Prob{response} = 1/(1+exp(-a - b × dose)) with $b \geq 0$

BMDS: Prob{response}= 1/(1+exp(-(α + β dose))) with $\beta \geq 0$

Equivalence in Parameters: $a = \alpha$, $b = \beta$

Starting values: as implemented in PROAST

9.3.3 RESTRICTED LOG-LOGISTIC MODEL

PROAST: Prob{response} = a + (1 - a)/(1 + exp(c × ln(b / dose))), with $0 \leq a \leq 1$, $b \geq 0$ and $c \geq 1$ in the restricted version.

BMDS: Prob{response}= $\gamma + (1 - \gamma)/(1+\exp(-(\alpha + \beta \ln(\text{dose}))))$, with $0 \leq \gamma \leq 1$, $\alpha \geq 0$ and $\beta \geq 1$ in the restricted version.

Equivalence in Parameters: $\alpha = - c \ln(b)$, $\beta = c$ and $\gamma = a$.

Starting values: as implemented in PROAST

9.3.4 RESTRICTED LOG-PROBIT MODEL

PROAST: Prob{response} = $a + (1 - a) \times \Phi(c \times \ln(\text{dose}/b))$, with $0 \leq a \leq 1$, $b \geq 0$ and $c \geq 1$ in the restricted version, where $\Phi(x)$ is the cumulative distribution of the standard normal distribution.

BMDS: Prob{response}= $\gamma + (1-\gamma) \times \Phi(\alpha + \beta \ln(\text{dose}))$, with $0 \leq \gamma \leq 1$ and $\beta \geq 1$ in the restricted version.

Equivalence in Parameters: $\alpha = - c \ln(b)$, $\beta = c$ and $\gamma = a$.

Starting values: as implemented in PROAST

9.3.5 PROBIT MODEL

PROAST: Prob{response} = $\Phi(b(\text{dose} - a))$

BMDS: Prob{response}= $\Phi(\alpha + \beta \text{ dose})$

Equivalence in Parameters: $\alpha = - ab$, $\beta = b$.

Starting values: as implemented in PROAST

9.3.6 RESTRICTED WEIBULL MODEL

PROAST: Prob{response} = $a + (1 - a)(1 - \exp(-(\text{dose}/b)^c))$, with $0 \leq a \leq 1$, $b \geq 0$ and $c \geq 1$ (restricted version).

BMDS: Prob{response}= $\gamma + (1 - \gamma)\ (1 - \exp(-\beta \text{ dose}^{\alpha}))$, with $0 \leq \gamma \leq 1$, $\alpha \geq 1$ (restricted version) and $\beta \geq 0$.

Equivalence in Parameters: $\alpha = c$, $\beta = (1/b)^c$ and $\gamma = a$.

Starting values: as implemented in PROAST

9.3.7 ONE-STAGE DOSE-RESPONSE MODEL

PROAST: Prob{response} = $a + (1 - a)(1 - \exp(-(\text{dose}/b)))$, with $0 \leq a \leq 1$, $b \geq 0$ (restricted version).

BMDS: Prob{response}= $\gamma + (1 - \gamma)(1 - \exp(-\beta \text{ dose}))$, with $0 \leq \gamma \leq 1$, $\beta \geq 0$ (restricted version).

Equivalence in Parameters: $\beta = (1/b)$ and $\gamma = a$.

Starting values: as implemented in PROAST

9.3.8 RESTRICTED DICHOTOMOUS HILL MODEL

PROAST: not implemented in distribution v.32.2

BMDS: Prob{response}= $v \times g + (v - v \times g)/(1 + \exp(-a - b \times \ln(\text{dose})))$, with $0 \leq v \leq 1$, $0 \leq g \leq 1$, $b \geq 0$ (restricted version).

Note that if v = 1, the dichotomous Hill model is a log logistic model

Starting values: as implemented in BMDS

9.4 MODEL WEIGHTING

The modeling approach used by the FDA to model the data from the Chen (2010a, 2010b) study of a cohort located in northeastern Taiwan employs a set of alternative mathematical models to estimate the risk from the estimated lifetime cancer incidence and doses presented in Table 3.3. The primary purpose of this modeling technique is to represent the uncertainty arising from model selection on the risk estimates in addition to the uncertainty arising from dose estimation and statistical sampling error. Four different approaches are discussed: a) single model representations, b) a best model approach that uses a single model for each individual bootstrap

data set that is selected by goodness of fit, c) an equiprobable weighting scheme where each alternative model gets equal weight, and d) a weight of the evidence approach where alternative models are evaluated by both goodness of fit and biological plausibility. All the simulation results shown below were generated using BMDS parameterization.

9.4.1 SINGLE MODEL SENSITIVITY ANALYSIS

The most common procedure for dealing with model uncertainty is to simply choose one model and justify that choice with nonscientific arguments, i.e. by tradition (e.g., using a "default" model) or regulatory policy (e.g. using a conservative model that will err on the side of safety). However, even when this approach is taken, the results of alternative models are often presented as sensitivity analyses. This section presents the results of eight different individual models, which illustrates the impact of using any one model to obtain the risk estimates.

Table 9.3. Baseline Risk Estimates with Lifetime Exposure

Exposure Estimate	Model	Bladder	Lung	Total[a]
Average Per Capita	Gamma	25.5 (9.9, 47.8)	40.7 (27.8, 62.2)	66.7 (43.4, 103.2)
Average Per Capita	Logistic	8.8 (5.3, 14.3)	25.3 (17.3, 38.6)	34.4 (23.6, 50.7)
Average Per Capita	Loglogistic	26.2 (9.5, 49.8)	42.5 (28.8, 65.4)	69.3 (45.0, 107.4)
Average Per Capita	Logprobit	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Average Per Capita	Probit	9.8 (5.8, 16.1)	27.1 (18.5, 41.3)	37.2 (25.5, 55.0)
Average Per Capita	Weibull	25.5 (10.0, 47.7)	40.7 (27.8, 62.2)	66.8 (43.4, 103.1)
Average Per Capita	One-Stage Dose-Response	26.5 (12.6, 48.1)	40.7 (27.8, 62.2)	67.7 (45.2, 103.9)
Average Per Capita	Hill Quantal	2.2 (0.0, 148.7)	0.0 (0.0, 0.0)	2.2 (0.0, 148.7)
3 Servings Brown	Gamma	386.0 (164.4, 721.0)	613.2 (418.3, 942.1)	1006.0 (659.7, 1566.1)
3 Servings Brown	Logistic	134.1 (80.3, 217.2)	382.6 (261.8, 584.6)	521.0 (356.6, 770.9)
3 Servings Brown	Loglogistic	398.4 (166.3, 748.4)	639.6 (434.4, 989.1)	1044.3 (685.1, 1625.9)
3 Servings Brown	Logprobit	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
3 Servings Brown	Probit	148.5 (88.0, 243.1)	409.3 (279.7, 625.9)	563.1 (384.2, 828.7)
3 Servings Brown	Weibull	386.0 (164.6, 721.0)	613.2 (418.3, 942.1)	1006.5 (659.9, 1566.1)
3 Servings Brown	One-Stage Dose-Response	399.5 (190.8, 723.9)	613.2 (418.3, 942.1)	1023.6 (679.2, 1566.2)
3 Servings Brown	Hill Quantal	245.5 (0.0, 2242.0)	0.0 (0.0, 0.0)	245.5 (0.0, 2242.0)

[a] Total cancer rates were estimated by adding lung and bladder estimates for each individual boostrap so the model for each endpoint is based on the same dose estimates. The same model used for both lung and bladder cancer.

Individual Dose-Response Models

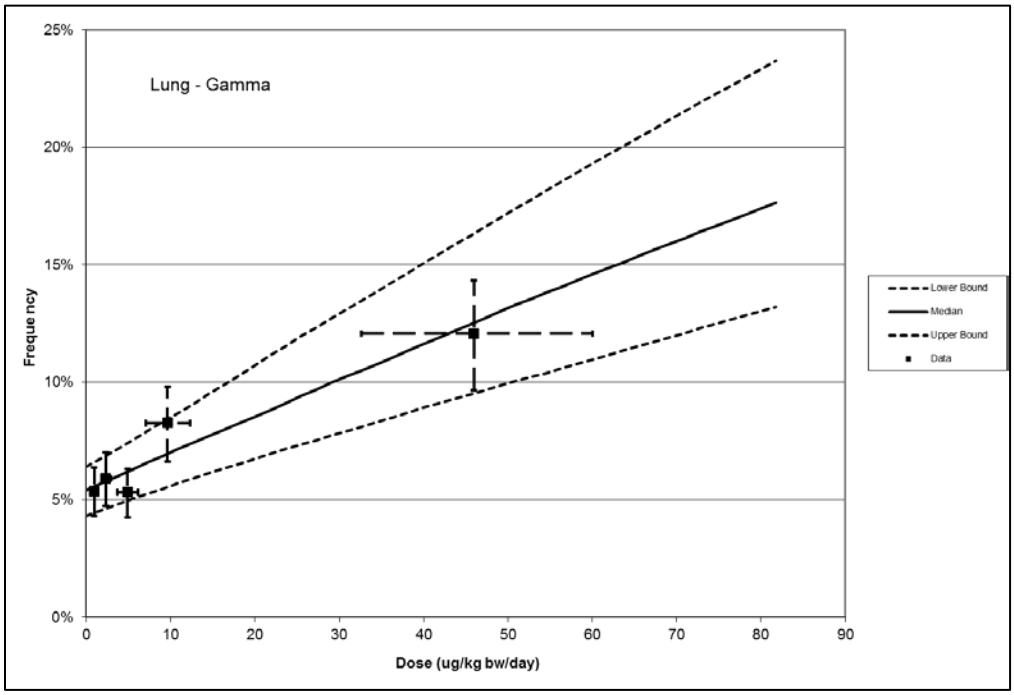


Figure 9.2. Gamma Dose-Response Model for Lung Cancer

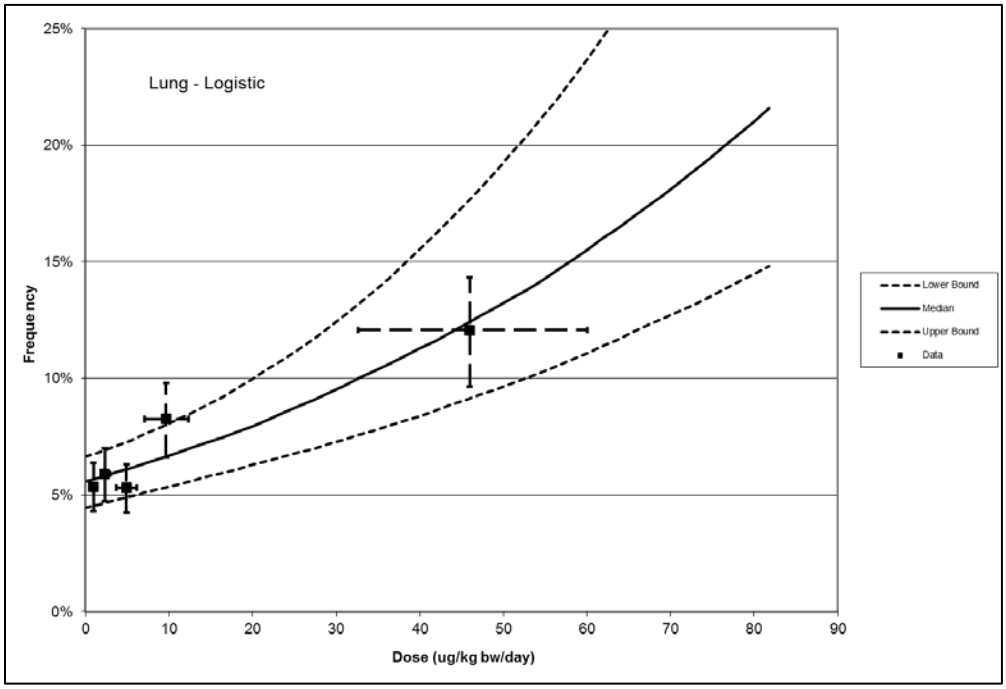


Figure 9.3. Logistic Dose-Response Model for Lung Cancer

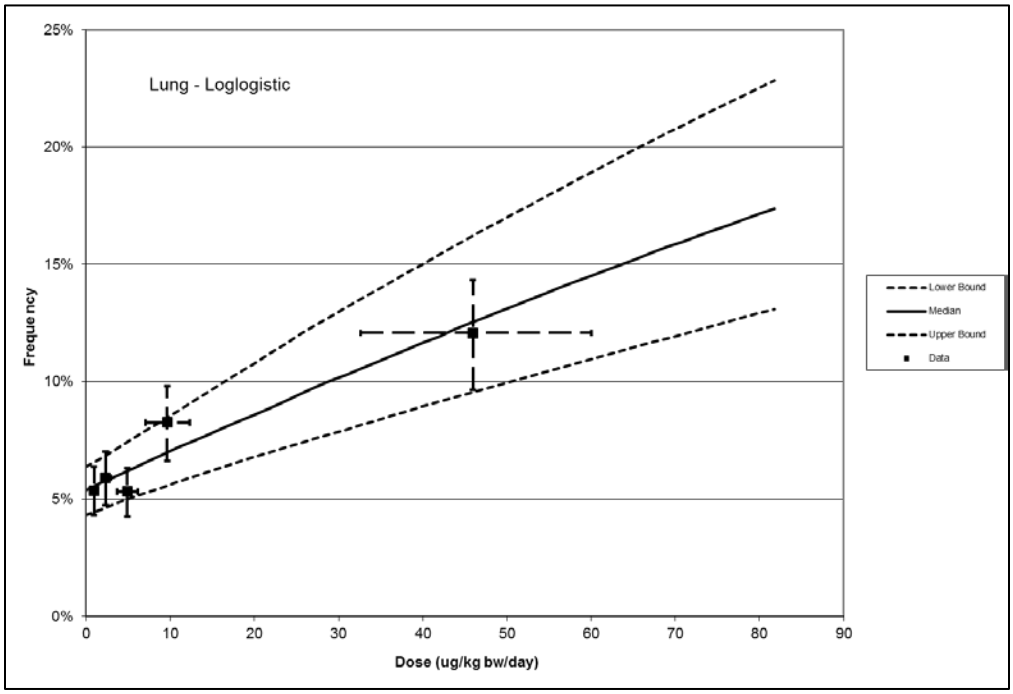


Figure 9.4. Loglogistic Dose-Response Model for Lung Cancer

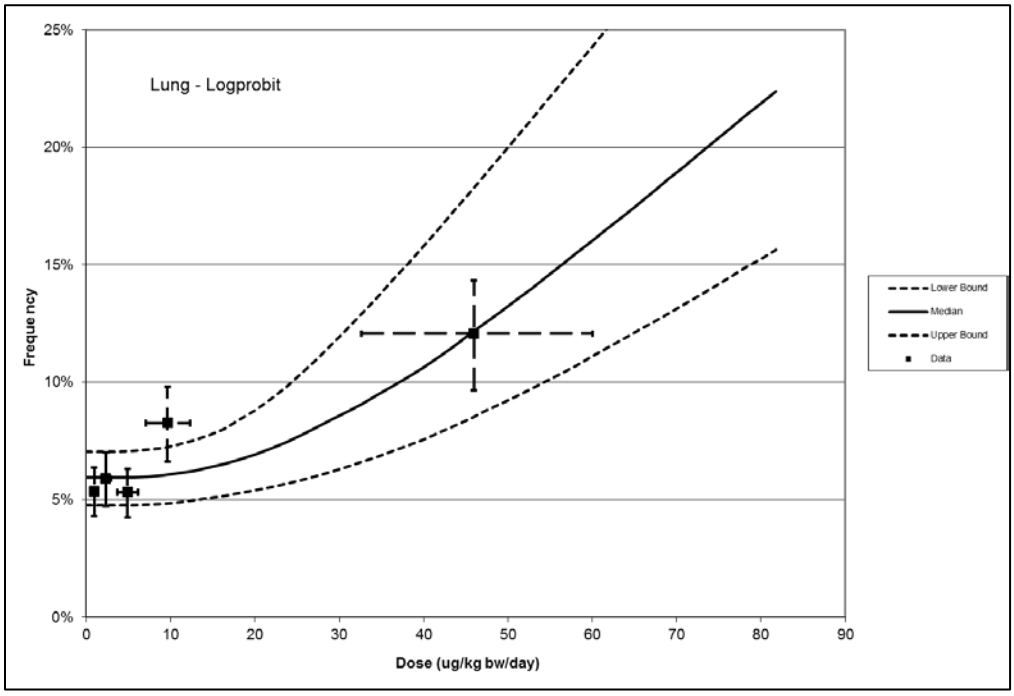


Figure 9.5. Logprobit Dose-Response Model for Lung Cancer

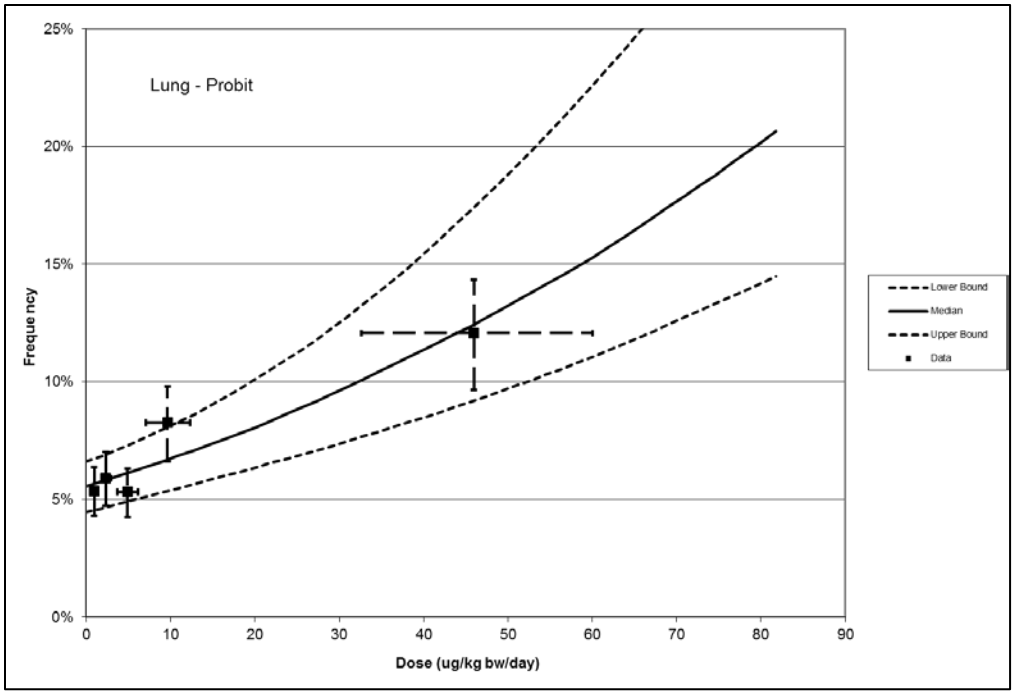


Figure 9.6. Probit Dose-Response Model for Lung Cancer

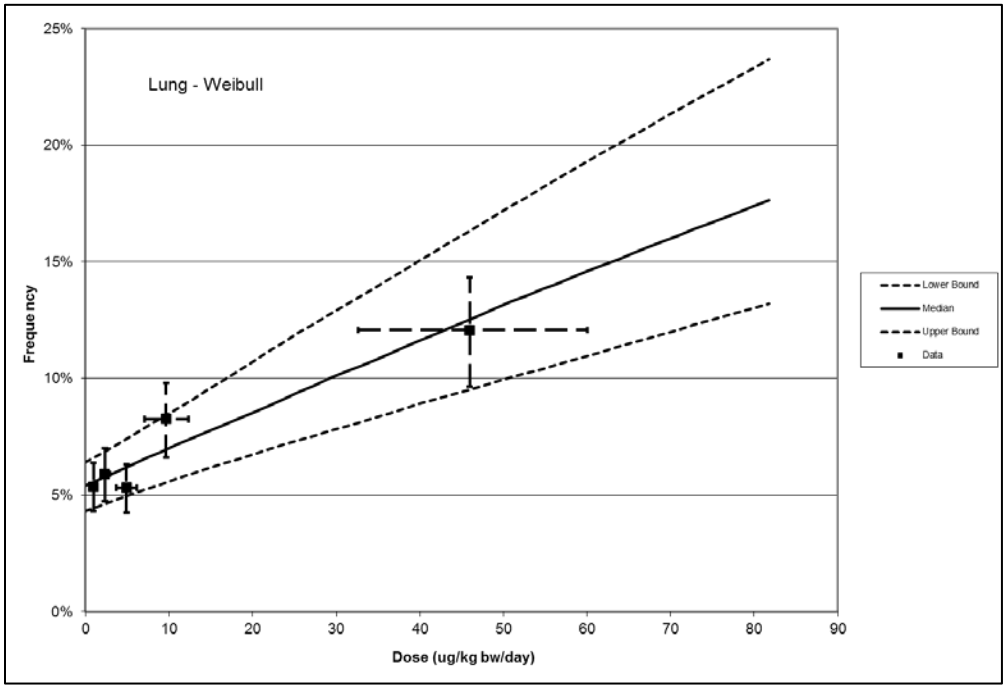


Figure 9.7. Weibull Dose-Response Model for Lung Cancer

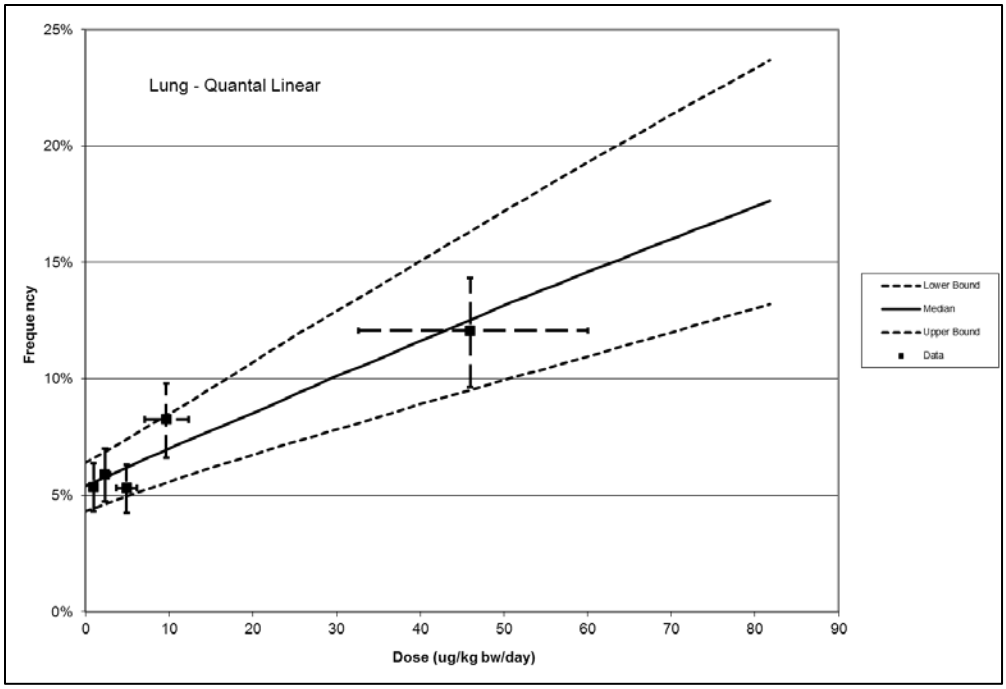


Figure 9.8. One-Stage Dose-Response Model for Lung Cancer

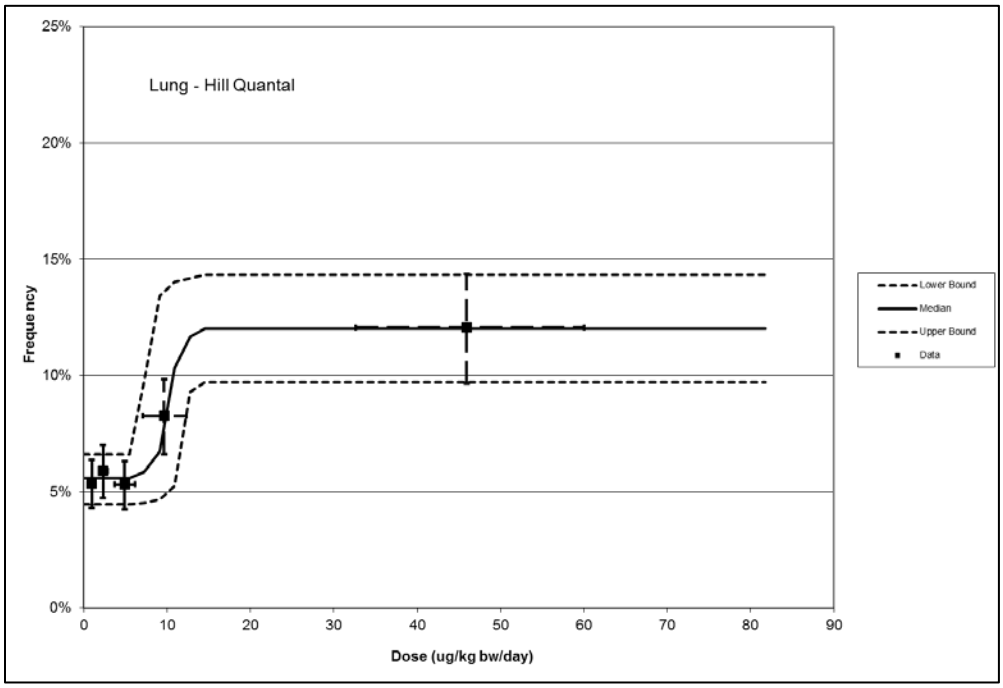


Figure 9.9. Hill Quantal Dose-Response Model for Lung Cancer

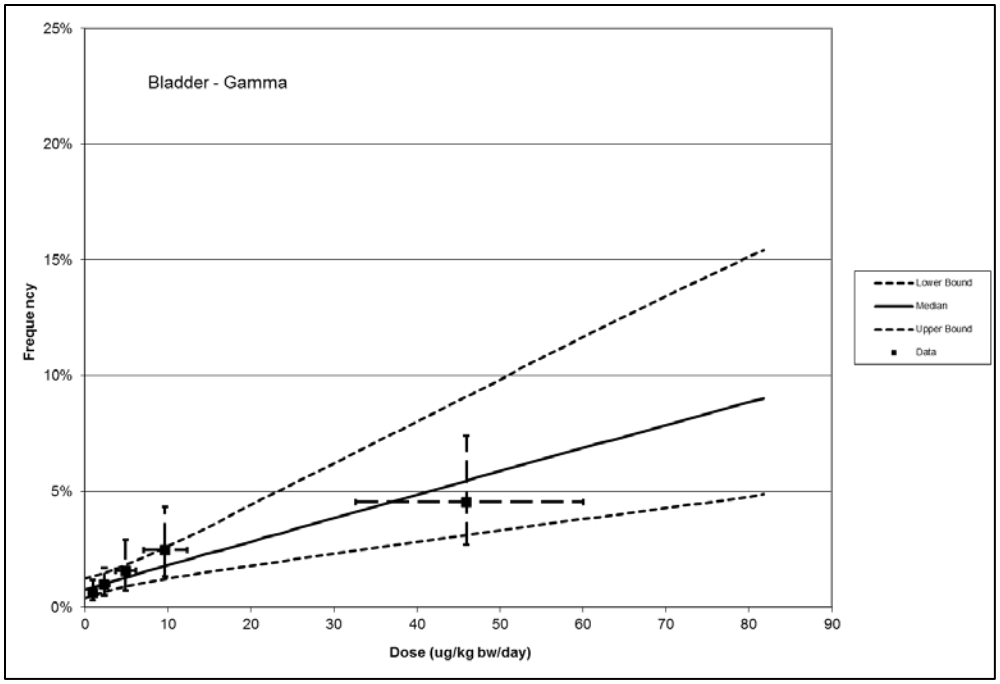


Figure 9.10. Gamma Dose-Response Model for Bladder Cancer

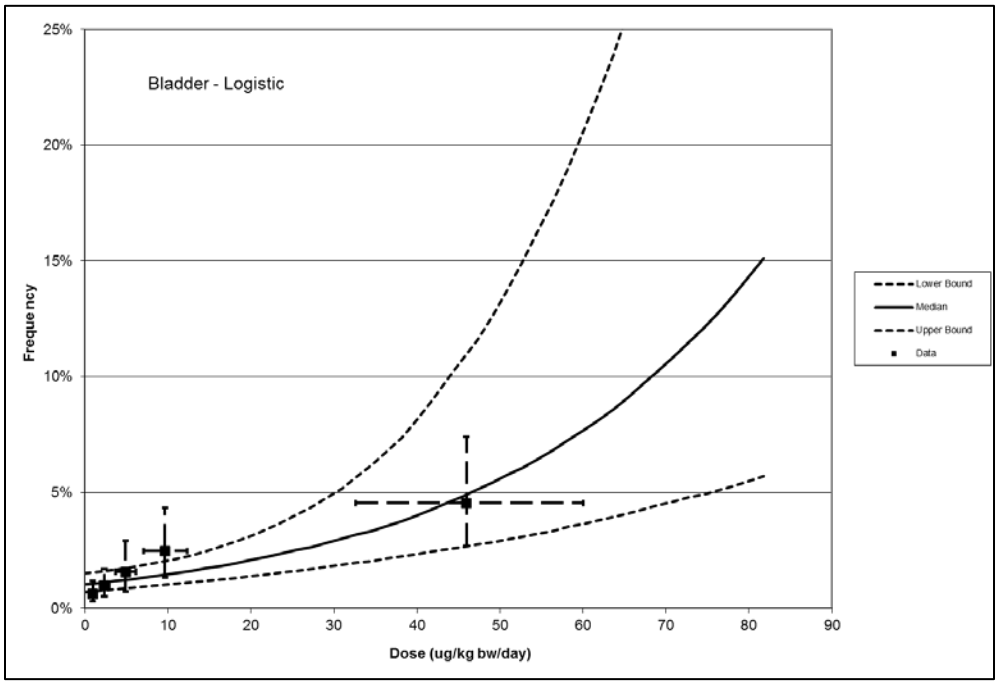


Figure 9.11. Logistic Dose-Response Model for Bladder Cancer

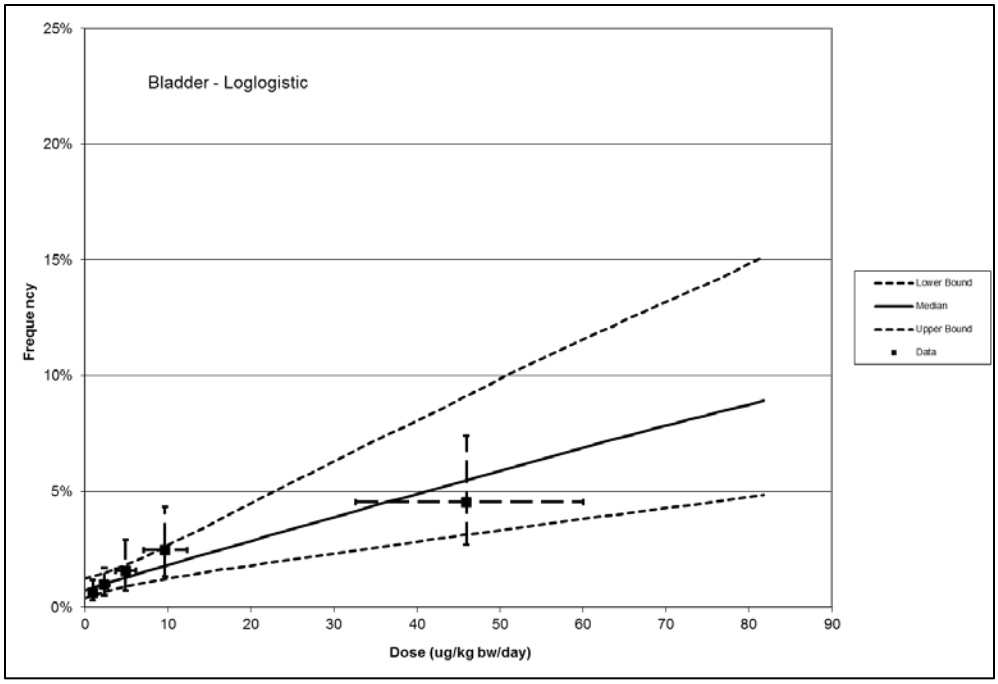


Figure 9.12. Loglogistic Dose-Response Model for Bladder Cancer

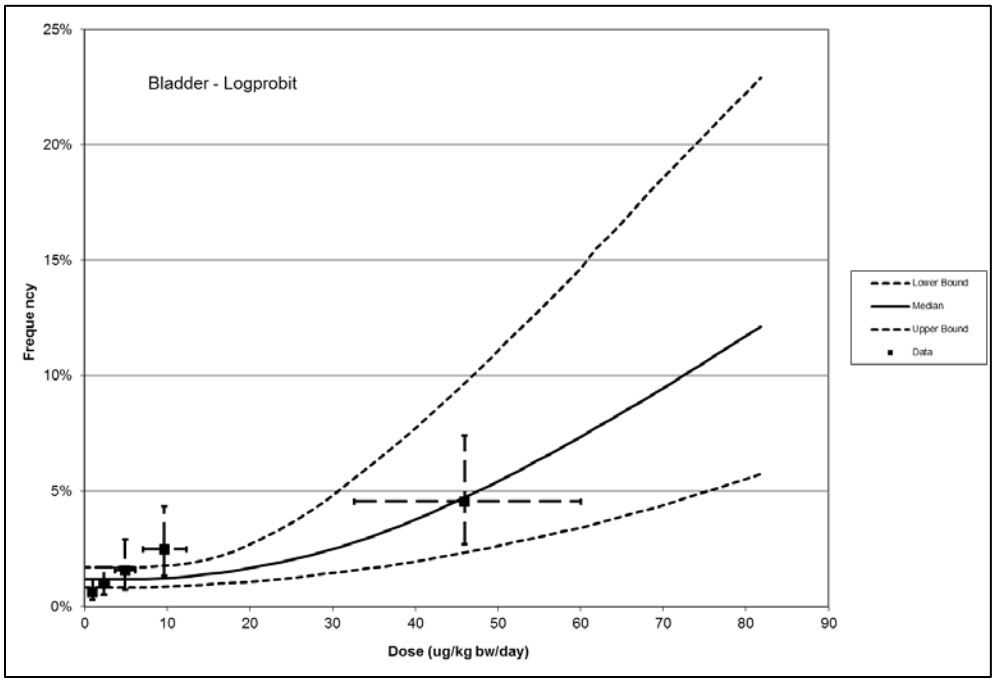


Figure 9.13. Logprobit Dose-Response Model for Bladder Cancer

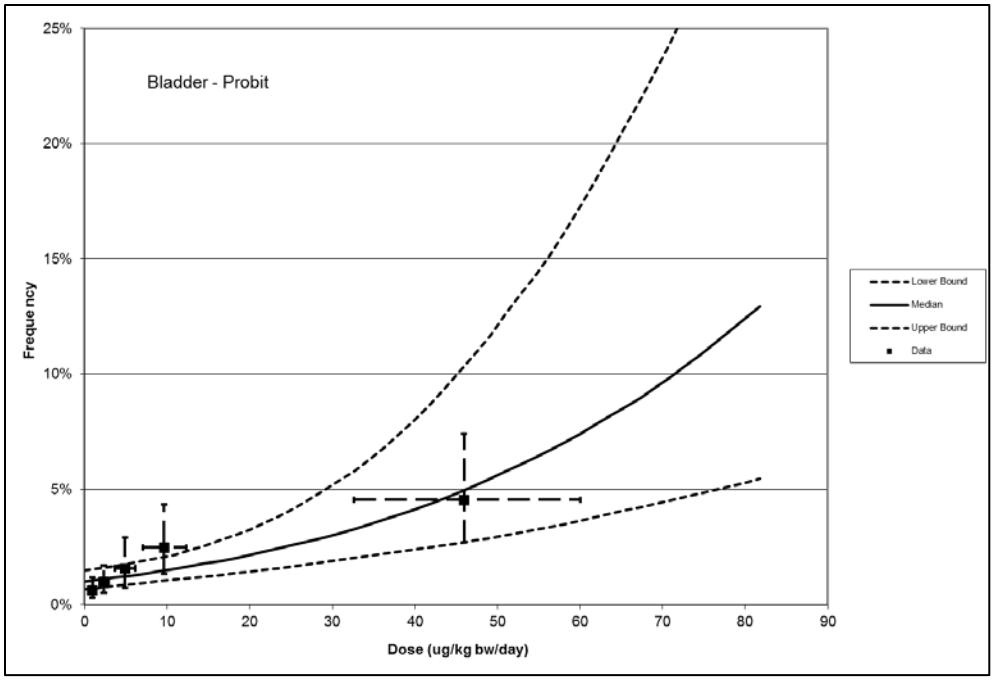


Figure 9.14. Probit Dose-Response Model for Bladder Cancer

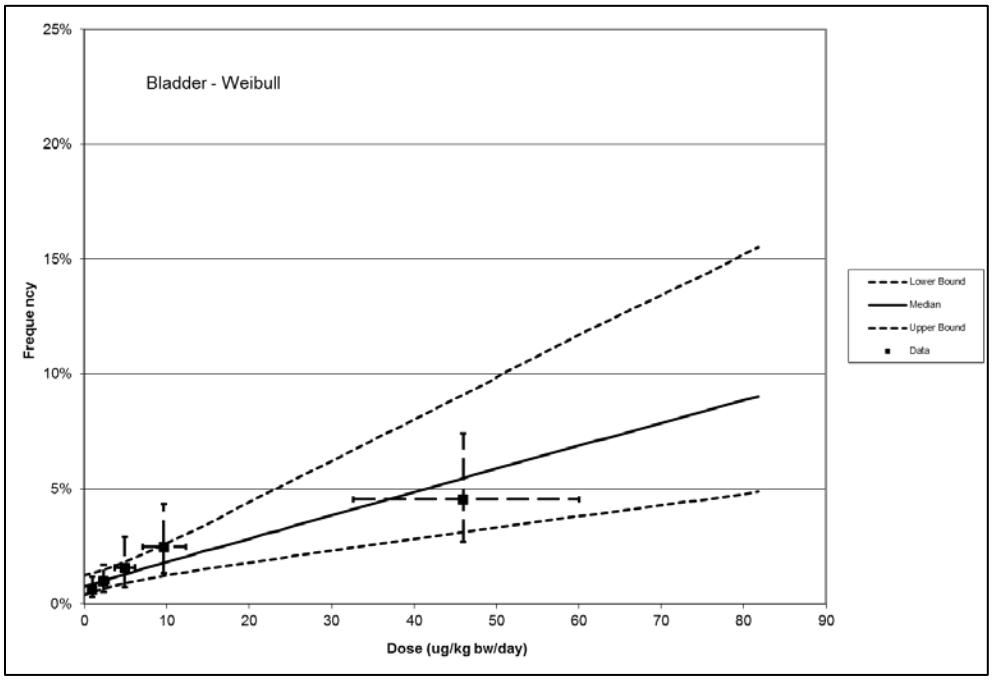


Figure 9.15. Weibull Dose-Response Model for Bladder Cancer

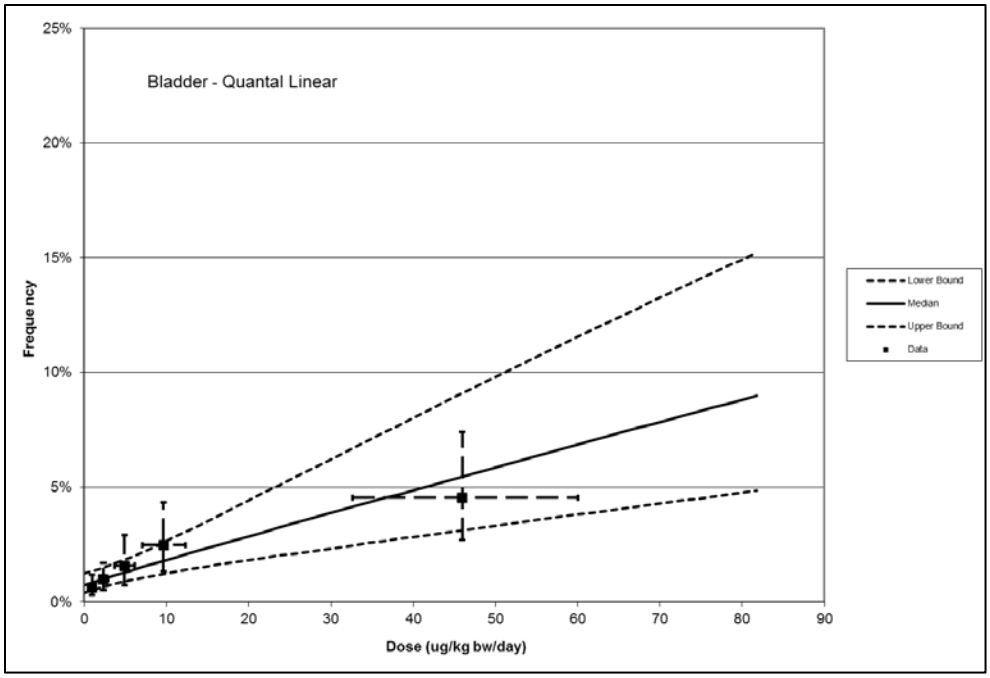


Figure 9.16. One-Stage Dose-Response Model for Bladder Cancer

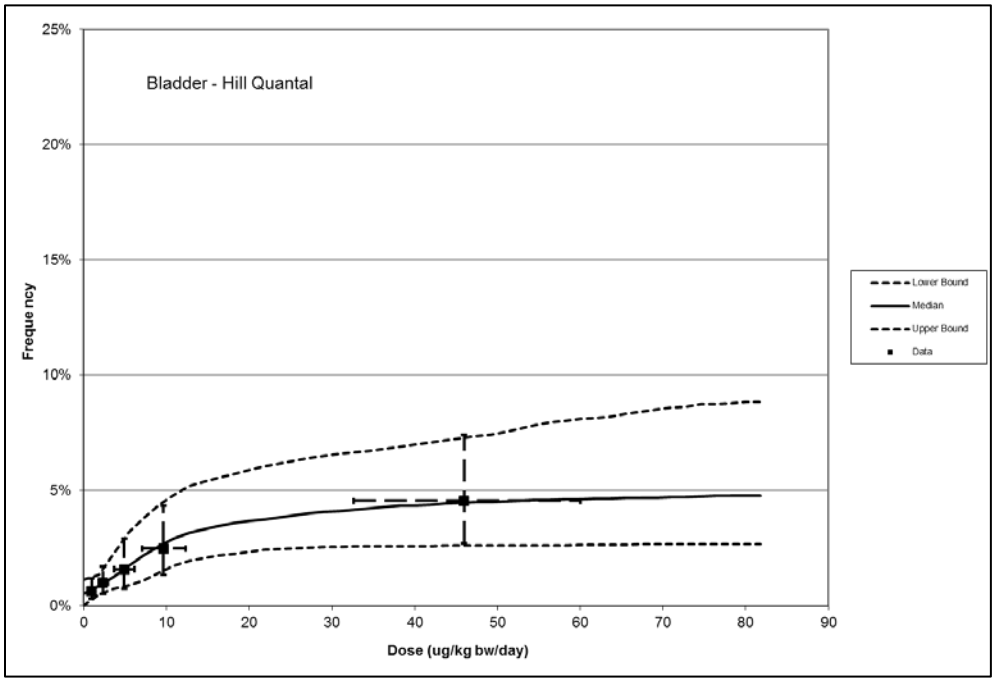


Figure 9.17. Hill Quantal Dose-Response Model for Bladder Cancer

It can be observed from the numerical estimates and the graphs that several of the models are nearly identical. The Gamma, Loglogistic, Weibill, and One-stage dose-response models are all nearly linear over the entire data range and yield risk estimates that are for all practical purposes are the same. The Logistic and Probit models are less linear and nearly identical to each other. The Logprobit and Quantal Hill models are both unique and highly nonlinear. The latter model is

especially distinctive in that it posits two subpopulations, only one of which is susceptible to arsenic.

Even though they represent the impact of model uncertainty, usually in a technical appendix such as this one, sensitivity analyses do not incorporate model uncertainty in to the decision process. For example, even though the original analysis by Morales *et al.* (2000) explored a number of different alterative models, only one was ultimately selected for inclusion in the cost-benefit analysis used to support the 2001 EPA Drinking Water Rule (EPA, 2001).

9.4.2 BEST MODEL

This approach, which was employed in the apple juice risk assessment (Carrington *et al.*, 2013), uses a goodness-of-fit criterion to select the best fitting model for each data bootstrap iteration. However, unlike the apple juice assessment, this assessment used the Akaike Information Criterion (AIC) to identify the best model instead of residual squares. Unlike residual squares, the AIC rewards models for fitting the data with fewer parameters.

The Akaike information criterion (AIC) was evaluated for each set for each of the 8 models at their ML estimates. This statistic is evaluated as AIC = 2*k* - 2*L*, where *k* is the number of parameters, and *L* is the maximized value of the log-likelihood function for the estimated model.The preferred model is the one with the minimum AIC value.

The number of parameters *k* was estimated as the number of parameters that did not reach a bound of their domain of definition. As an example, the gamma model is a three-parameter model. If the maximum likelihood is obtained with a value *c* = 1, then the AIC is evaluated using *k* = 2, assuming that the model tested was Prob{response} = *a* + (1 - *a*) pgamma(*b* dose; 1), rather than Prob{response} = *a* + (1 - *a*) pgamma(*b* dose; *c*).

Table 9.4. Best Model Risk Estimates

Exposure Estimate	Model	Bladder	Lung	Total[a]
Average Per Capita	Best 1	13.3 (0.0, 147.8)	40.3 (26.5, 61.0)	55.2 (29.2, 191.0)
Average Per Capita	Best 2	13.7 (0.0, 147.8)	42.3 (28.1, 64.9)	57.9 (31.1, 193.2)
3 Servings Brown	Best 1	299.8 (0.0, 2242.0)	607.2 (397.9, 925.1)	903.4 (450.0, 2878.8)
3 Servings Brown	Best 2	307.2 (0.0, 2242.0)	638.5 (421.1, 985.2)	948.7 (488.9, 2920.0)

[a] Total cancer rates were estimated by adding lung and bladder estimates for each individual boostrap so the model for each endpoint is based on the same dose estimates. Since the "best" model can differ for each endpoint, the models used for lung and bladder cancer were not necessarily the same.

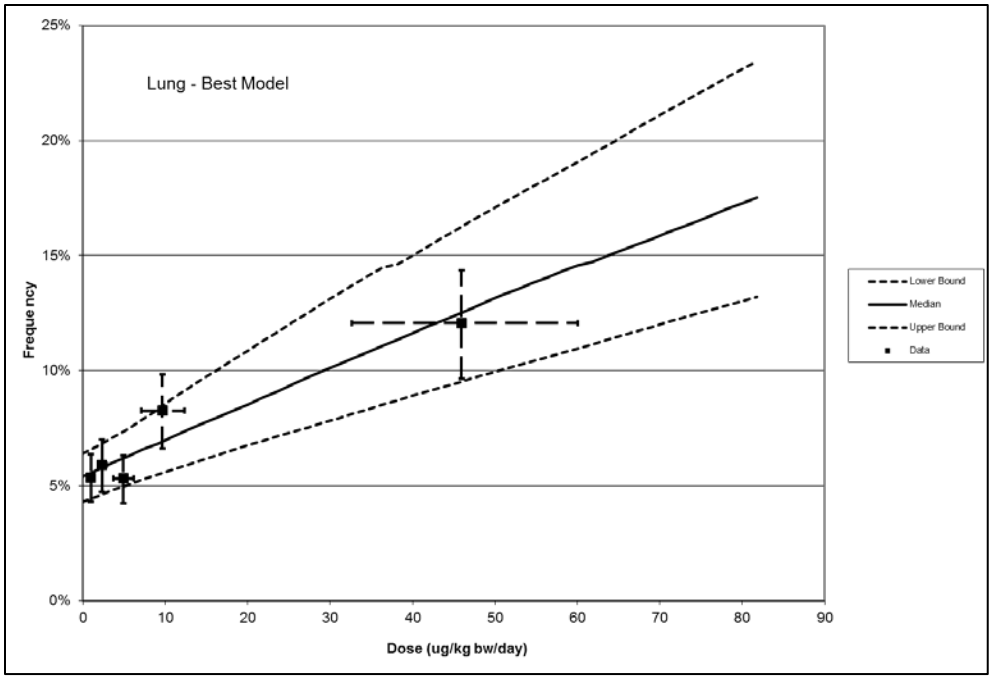


Figure 9.18. Best Dose-Response Model for Lung Cancer

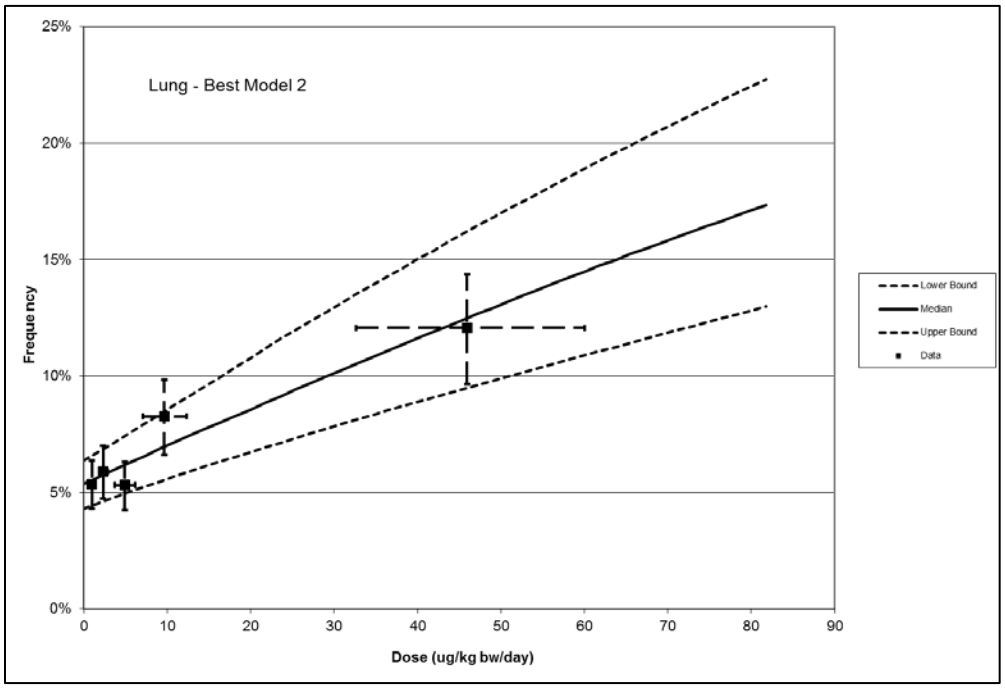


Figure 9.19. Best Dose-Response Model #2 for Lung Cancer

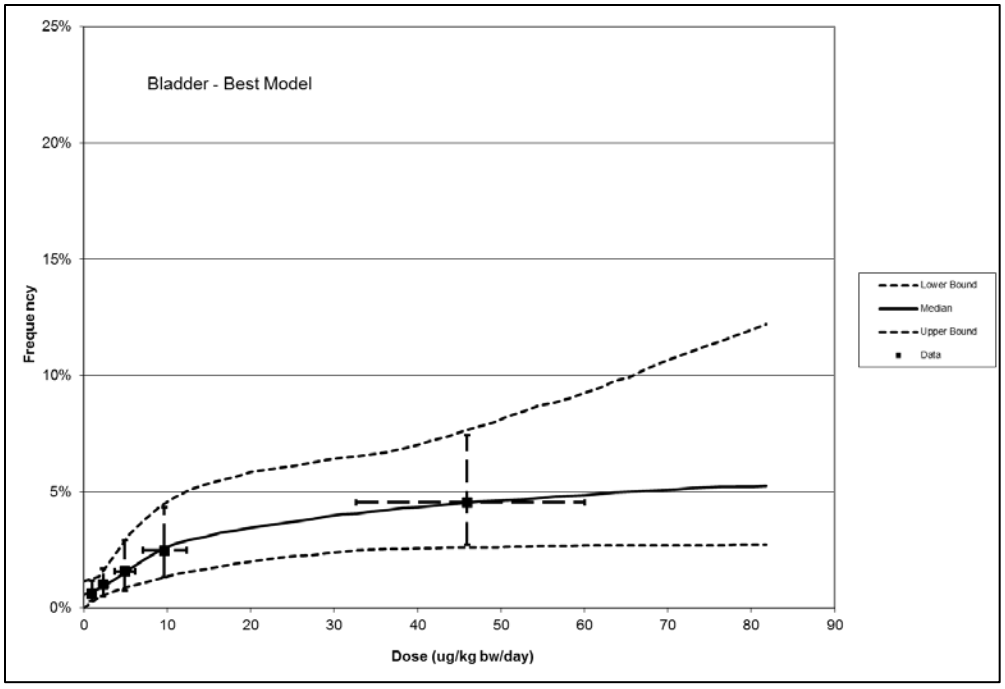


Figure 9.20. Best Dose-Response Model for Bladder Cancer

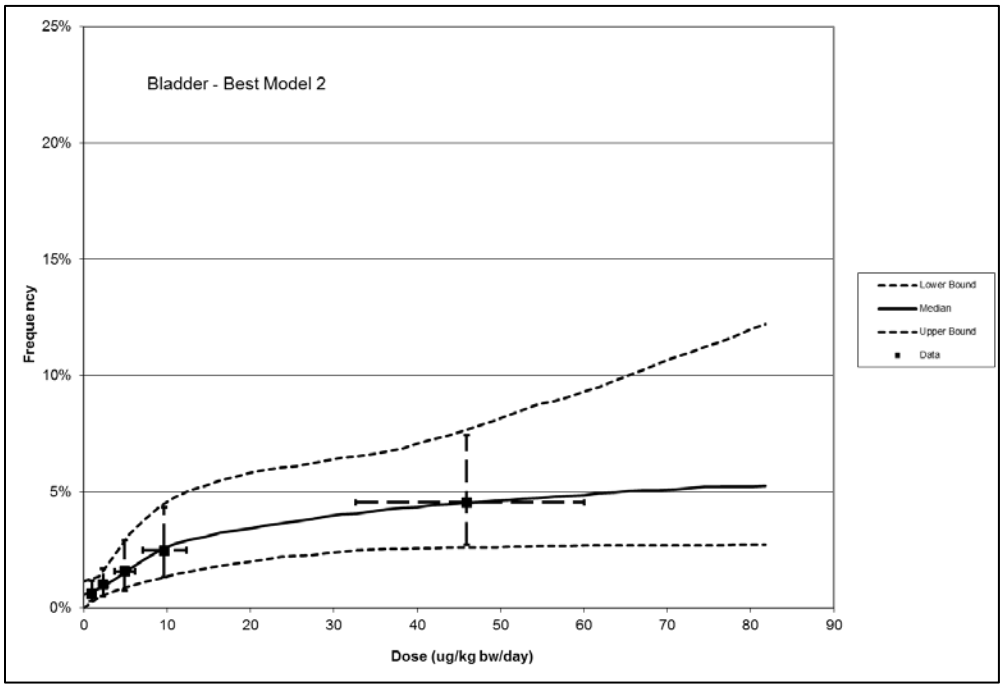


Figure 9.21. Best Dose-Response Model #2 for Bladder Cancer

It may be observed from the graphs that the dose-response function for lung cancer is dominated by the linear models, while the function for bladder cancer is dominated by the Quantal Hill model. A shortcoming of using the best model approach, even when used in conjunction with

data bootstrapping, is that is tends to favor one model over all others even when the difference in the quality of fit is very small.

9.4.3 EQUIPROBABLE MODELS

If the data have limited power to discriminate between potential dose response models, a number of different alternative can be used to characterize model uncertainty, with each model given equal weight. The following tables and graphs illustrate the risk estimates and dose response function that result from this approach using the four different model forms (Logprobit, Probit, Weibull, and Hill) that resulted from the initial set of eight.

Table 9.5. Risk Estimates Accounting for Model Uncertainty

Exposure Estimate		Bladder	Lung	Total[a]
Average Per Capita	All Rice	9.1 (0.0, 72.8)	7.7 (0.0, 51.3)	31.0 (0.0, 98.8)
3 Servings	Brown Other	125.5 (0.0, 1065.2)	96.6 (0.0, 651.1)	406.2 (0.0, 1341.7)

[a] Total cancer rates were estimated by adding lung and bladder estimates for each individual boostrap so the model for each endpoint is based on the same dose estimates. The same model used for both lung and bladder cancer.

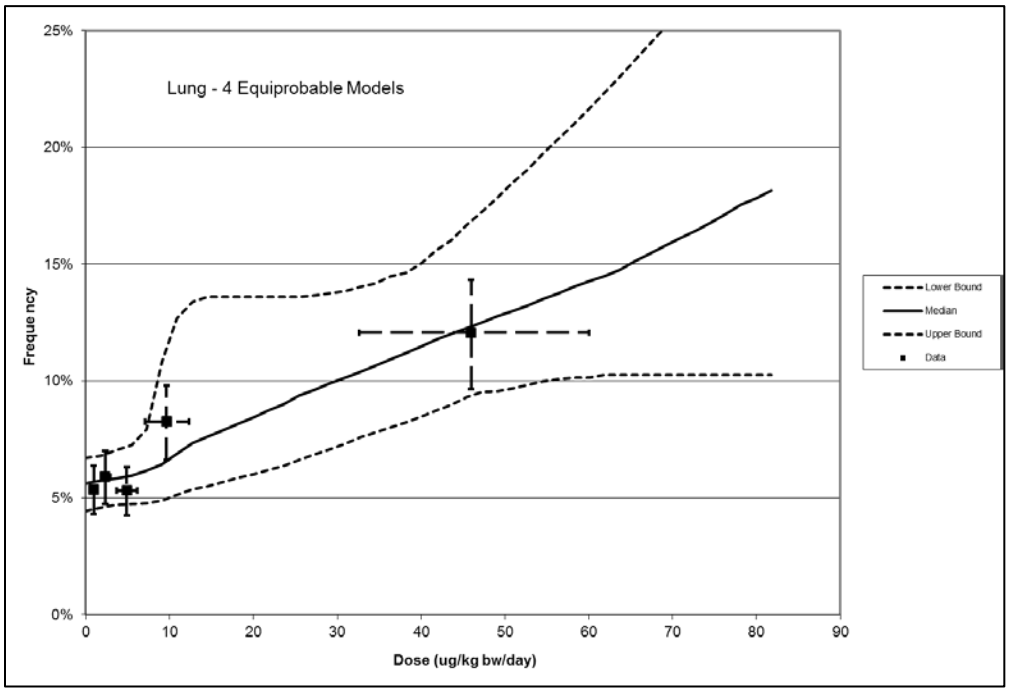


Figure 9.22. Four Equiprobable Models for Lung Cancer

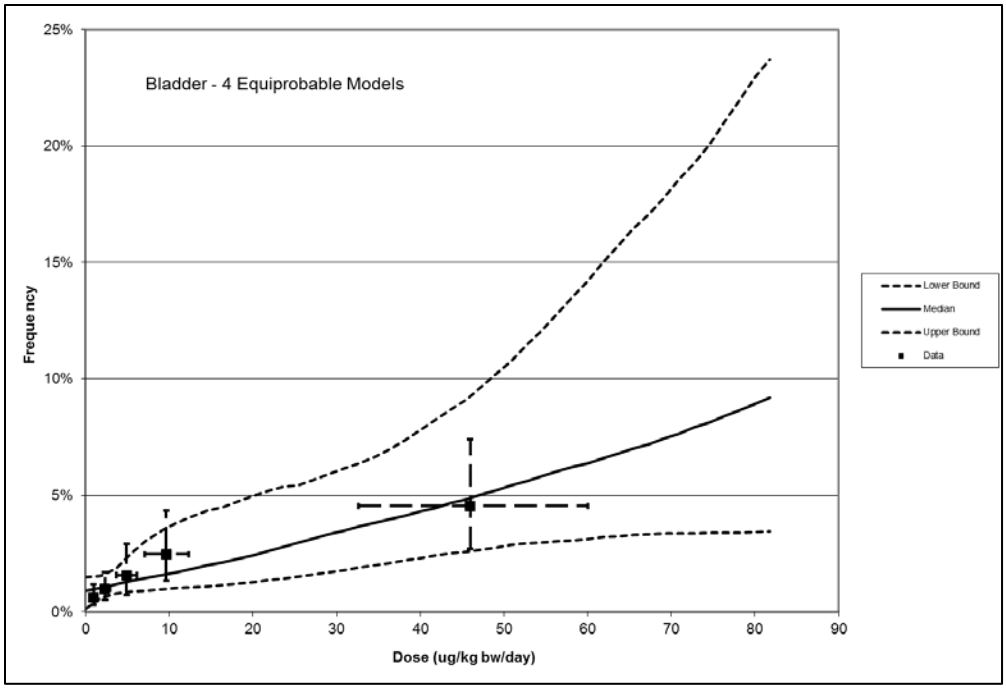


Figure 9.23. Four Equiprobable Models for Bladder Cancer

9.4.4 WEIGHT OF THE EVIDENCE

In addition to considering empirical fit, scientific evidence can be used to give some models more weight than others. This allows theory and knowledge from other sources to be considered. This technique is inherently subjective and therefore generally relies on expert opinion to establish relative weights of alternative models. Although the weight of the evidence approach can be employed through expert elicitation (e.g., David *et al.*, 1975; Evans *et al.*, 1994), a simplified approach that considers empirical fit, biological plausibility and theoretical support from other studies is employed here.

Table 9.6. Weight of Evidence to Determine Best Dose-Response Model

Model	Empirical fit (AIC)	Plausibility	Mechanistic support, counter support
Linear (e.g. Weibull)	Best for lung, also good for bladder	Consistent with genotoxic mechanism or additive effects	Low dose effects on lung support additive effect
Sublinear (Probit)	Good, but not best for both lung and bladder	Consistent with non genotoxic mechanism and significant population variability or additive effects	Low dose effects on lung support additive effect

Model	Empirical fit (AIC)	Plausibility	Mechanistic support, counter support
Highly Nonlinear (Logprobit)	Good for bladder, Poor for lung	Consistent with non genotoxic mechanism and limited population variability	Support from micronucleus paper
Sigmoidal (Hill)	Best for bladder, good for lung	Ascribes all risk to small subset of population, which is implausible	Smokers and/or genetic subpopulation may bear all of the risk

Conclusion: There is more support for a linear model for the lung. There is some support for a nonlinear mechanism for bladder. Three proposed weights for the four alternative models are given below. All three approaches give more weight to the linear models for the lung cancer dose-response function, and somewhat more nonlinear character to the dose-response function for bladder cancer.

For all three weighting schemes shown below, total cancer rates were estimated by adding lung and bladder estimates for each individual boostrap so the model for each endpoint is based on the same dose estimates. Since the model weighting for each endpoint was considered separately, the models used for each bootstrap were selected independently.

Approach #1:

Table 9.7. Approach #1: Model Options for Lung and Bladder Cancer Dose-Response Models

Model	Lung	Bladder
Linear	50%	30%
Sublinear	30%	30%
Nonlinear	20%	20%
Sigmoidal	0%	20%

Table 9.8. Approach #1: Lifetime Cancer Cases per Million

Exposure Estimate	Bladder	Lung	Total
Average Per Capita, All Rice	10.3 (0.0, 60.0)	32.2 (0.0, 58.1)	44.4 (0.1, 99.7)
3 Servings, Brown Other	140.0 (0.0, 912.4)	413.8 (0.0, 747.5)	569.5 (24.3, 1367.3)

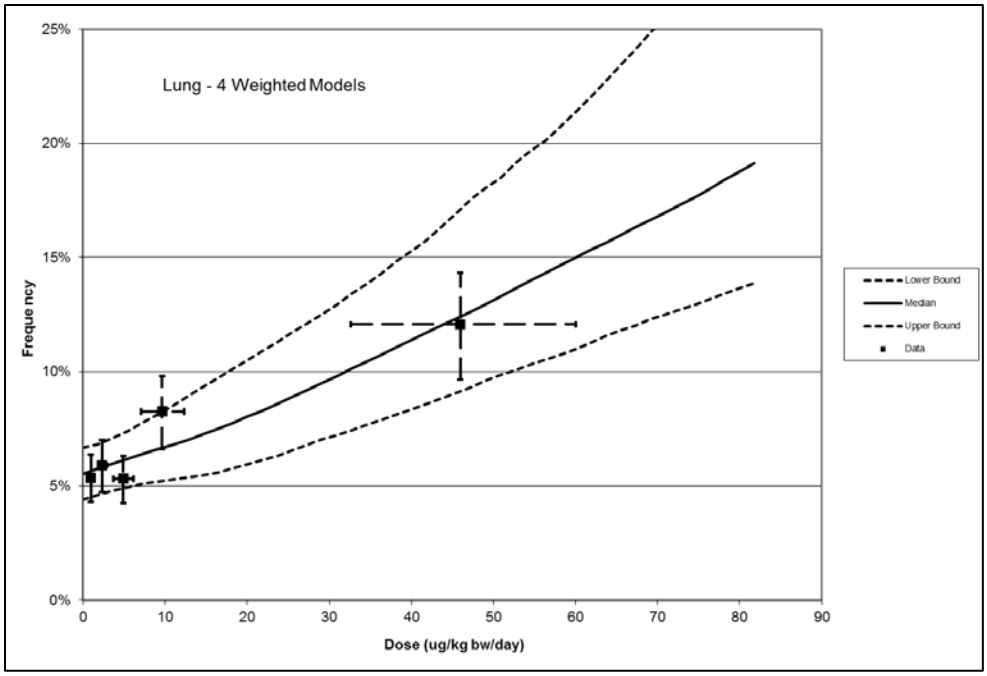


Figure 9.24. Approach #1: Four Weighted Models for Lung Cancer

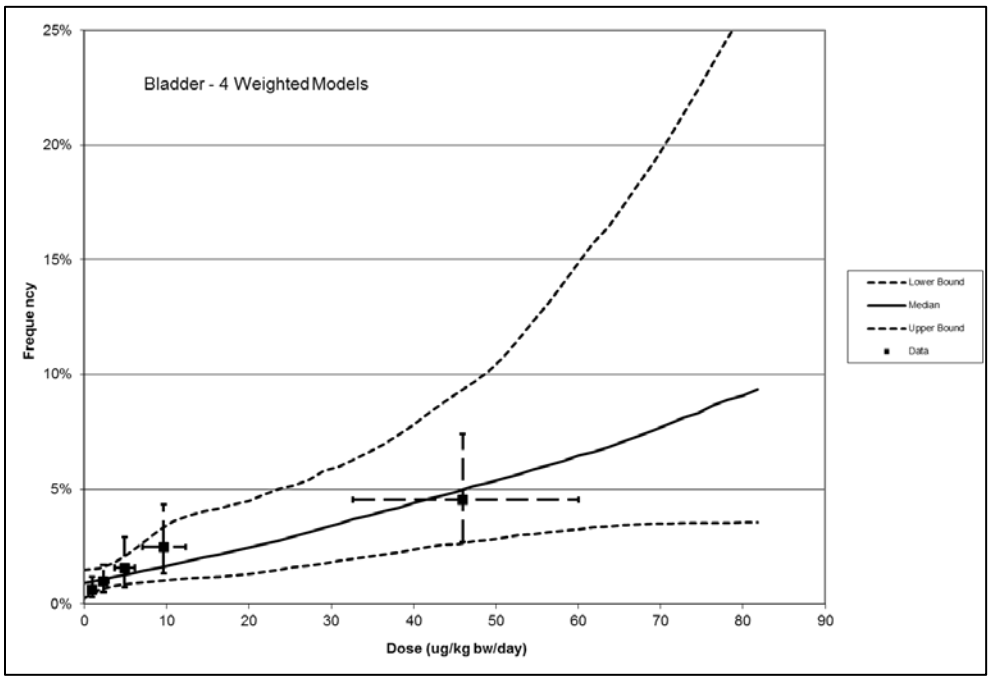


Figure 9.25. Approach #1: Four Weighted Models for Bladder Cancer

Approach #2:

Table 9.9. Approach #2: Model Options for Lung and Bladder Cancer Dose-Response Models

Model	Lung	Bladder
Linear	40%	30%
Sublinear	30%	40%
Nonlinear	30%	30%
Sigmoidal	0%	0%

Table 9.10. Approach #2: Lifetime Cancer Cases per Million

Exposure Estimate	Bladder	Lung	Total
Average Per Capita, All Rice	9.6 (0.0, 39.1)	28.1 (0.0, 55.7)	38.8 (0.0, 79.1)
3 Servings, Brown Other	122.3 (0.0, 500.8)	364.6 (0.0, 714.9)	494.9 (0.0, 1019.1)

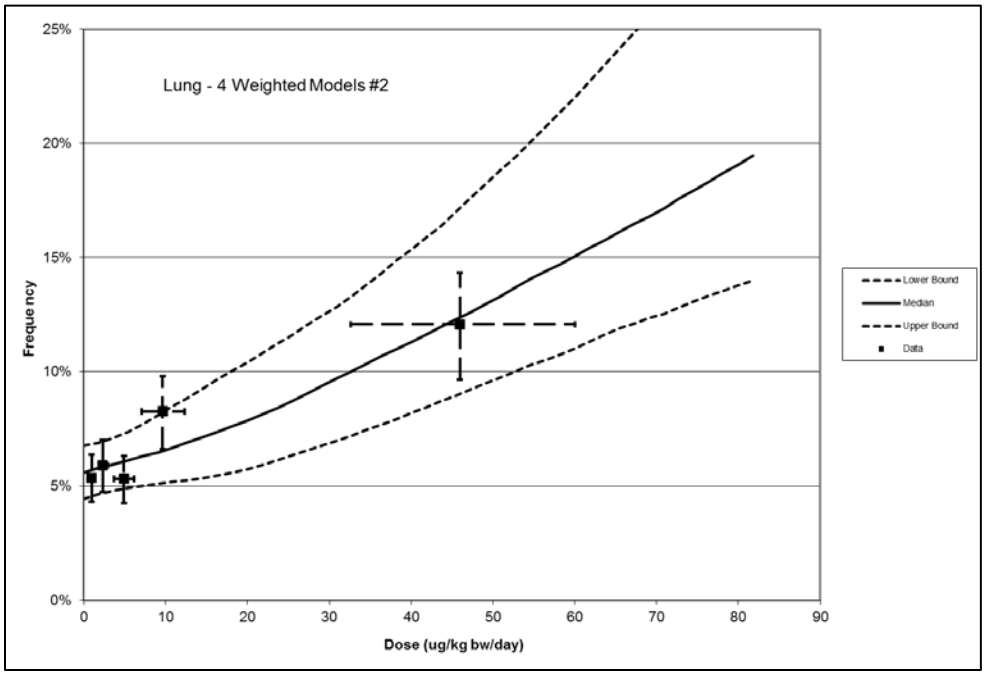


Figure 9.26. Approach #2: Four Weighted Models for Lung Cancer

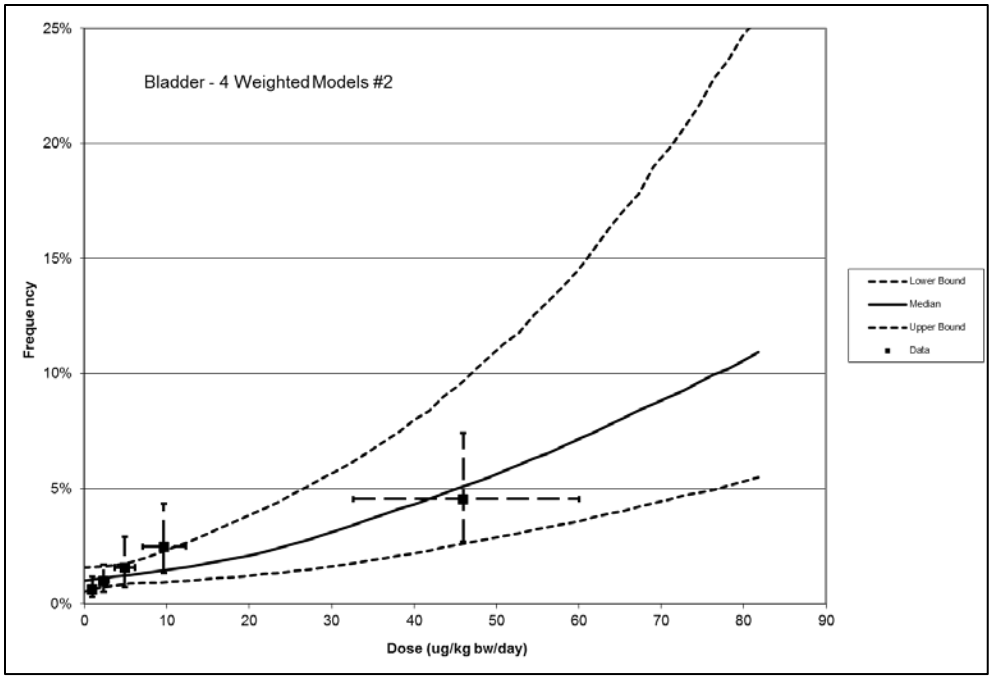


Figure 9.27. Approach #2: Four Weighted Models for Bladder Cancer

Approach #3:

Table 9.11. Approach #3: Model Options for Lung and Bladder Cancer Dose-Response Models

Model	Lung	Bladder
Linear	50%	30%
Sublinear	30%	40%
Nonlinear	10%	20%
Sigmoidal	10%	10%

Table 9.12. Approach #3: Lifetime Cancer Cases per Million

Exposure Estimate	Bladder	Lung	Total
Average Per Capita, All Rice	10.3 (0.0, 47.5)	31.9 (0.0, 58.1)	43.1 (4.8, 90.4)
3 Servings, Brown Other	134.7 (0.0, 617.8)	409.3 (0.0, 747.5)	557.0 (68.0, 1171.8)

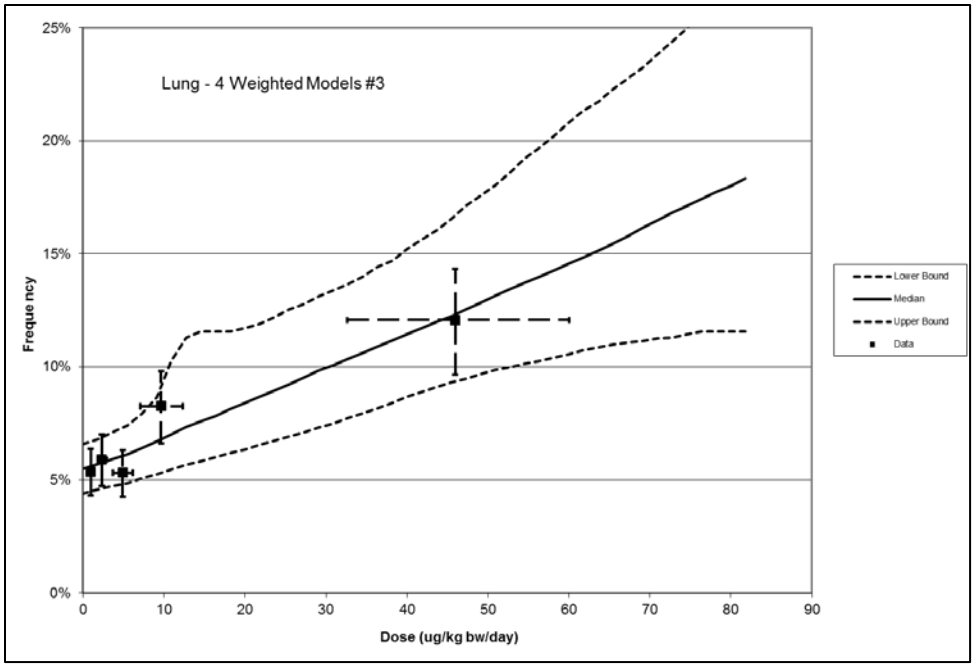


Figure 9.28. Approach #3: Four Weighted Models for Lung Cancer

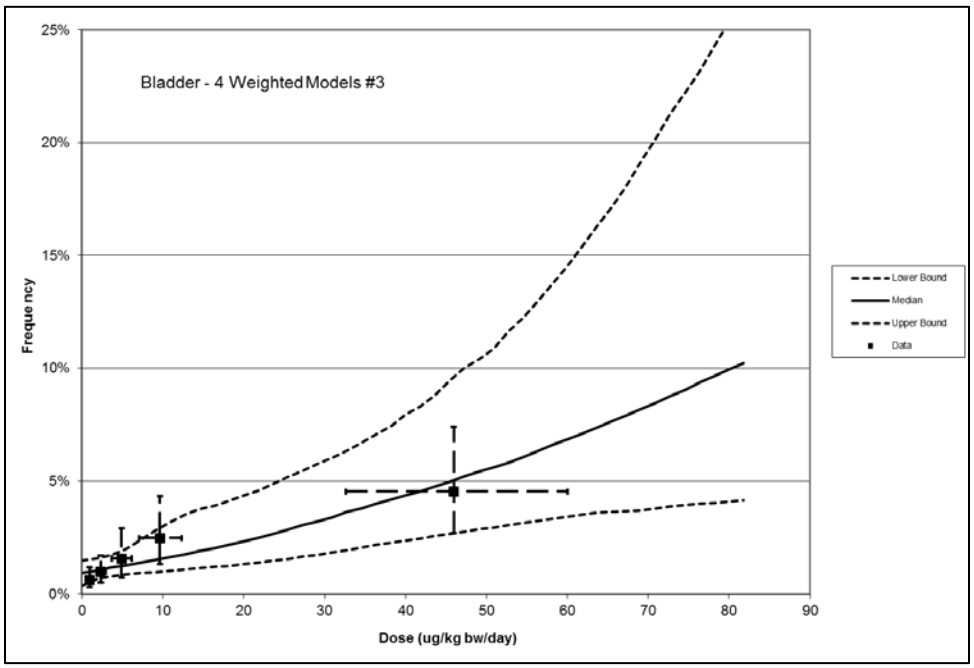


Figure 9.29. Approach #3: Four Weighted Models for Bladder Cancer

The estimates in the main body use proposal #2.

9.5 ARSENIC IN RICE AND RICE PRODUCTS (FDA 2013 AND 2016 DATA SURVEY)

Table 9.13. Summary Table – Arsenic in Rice (FDA, 2013)

Product Category	Average Total Arsenic ppb[a] (n)[b]	Range of Total Arsenic ppb (n)	Average Inorganic Arsenic ppb (n)	Range of Inorganic Arsenic ppb (n)	Average DMA[c] ppb (n)	Range of DMA ppb (n)	Average MMA[d] ppb (n)	Range of MMA ppb (n)	Total Number of Samples
Brown Basmati	188 (13)	84 – 448 (13)	123 (13)	66 – 200 (13)	68 (13)	15 – 324 (13)	6 (13)	3 – 11 (13)	13
White Basmati	114 (40)	40 – 526 (40)	62 (40)	20 – 144 (40)	48 (40)	14 – 382 (40)	7 (40)	3 – 12 (40)	40
Brown Long/medium/ short grain	272 (98)	57 – 854 (98)	161 (98)	34 – 249 (98)	107 (98)	11 – 568 (98)	7 (80)	1 – 25 (80)	98
Brown Instant	148 (2)	110 – 185 (2)	72 (2)	65 – 79 (2)	65 (2)	46 – 83 (2)	< LOD	< LOD	2
White Instant	141 (14)	90 – 244 (14)	58 (14)	31 – 134 (14)	85 (14)	50 – 189 (14)	3 (11)	2 – 5 (11)	14
Brown Jasmine	225 (2)	225 (2)	133 (2)	114 – 151 (2)	43 (2)	35 – 51 (2)	4 (1)	4 (1)	2
White Jasmine	136 (11)	63 – 185 (11)	78 (11)	34 – 110 (11)	46 (11)	14 – 87 (11)	< LOD	< LOD	11
Other (incl wild rice[e], carnaroli, mixed types)	157 (6)	112 – 227 (6)	124 (6)	88 – 161 (6)	32 (6)	8 – 70 (6)	< LOD	< LOD	6
Brown Parboiled	309 (1)	309 (1)	191 (1)	191 (1)	119 (1)	119 (1)	< LOD	< LOD	1
White Parboiled	215 (38)	91 – 362 (38)	112 (38)	71 – 182 (38)	98 (38)	17 – 188 (38)	3 (35)	2 – 8 (35)	38
White Long grain	243 (149)	74 – 776 (149)	103 (149)	23 – 196 (149)	131 (149)	37 – 687 (149)	5 (82)	1 – 23 (82)	149
White Medium grain	208 (91)	54 – 717 (91)	81 (91)	39 – 174 (91)	106 (91)	10 – 572 (91)	4 (52)	1 – 15 (52)	91
White Short grain	123 (23)	79 – 180 (23)	79 (23)	52 – 102 (23)	38 (23)	18 – 116 (23)	1 (16)	1 – 3 (16)	23

Note: The FDA samples were composites of six subsamples each; in some cases the sub-samples were taken from six packages with identical lot numbers, in some cases the subsamples were taken from six packages with different lot numbers, and in some cases the subsamples were taken from a single package.

[a] ppb = parts per billion (microgram/kilogram)

[b] n = number of samples used in the calculation

[c] DMA = dimethylarsinic acid

[d] MMA = monomethylarsonic acid

[e] "Wild rice" is not actual rice. Wild rice comes from an aquatic annual grass (*Zizania aquatic*) bearing edible grain.

Table 9.14. Summary Table – Arsenic in Rice Products (FDA, 2013)

Product Category	Average Total Arsenic ppb[a] (n)[b]	Range of Total Arsenic ppb (n)	Average Inorganic Arsenic ppb (n)	Range of Inorganic Arsenic ppb (n)	Average DMA[c] ppb (n)	Range of DMA ppb (n)	Average MMA[d] ppb (n)	Range of MMA ppb (n)	Total Number of Samples
Brownies	46 (5)	30 – 80 (5)	32 (5)	21 – 40 (5)	11 (5)	8 – 18 (5)	< LOD	< LOD	5
Cakes/Muffins	67 (22)	20 – 210 (22)	42 (24)	1 – 122 (24)	19 (21)	5 – 104 (21)	< LOD	< LOD	24
Pie and Pizza Crust	120 (3)	50 – 250 (3)	57 (3)	46 – 72 (3)	54 (3)	14 – 128 (3)	< LOD	< LOD	3
Pudding	100 (2)	80 – 120 (2)	27 (4)	1 – 80 (4)	55 (2)	50 – 59 (2)	< LOD	< LOD	4
Beer[e]	9 (65)	2 – 30 (65)	6 (65)	1 – 26 (65)	8 (1)	8 (1)	< LOD	< LOD	65
Non-Dairy Rice Drinks[e]	27 (61)	6 – 131 (61)	14 (61)	3 – 46 (61)	15 (32)	1 – 45 (32)	2 (2)	1 – 2 (2)	61
Protein Beverages[e]	80 (32)	4 – 260 (32)	50 (32)	2 – 107 (32)	21 (13)	9 – 79 (13)	7 (3)	5 – 8 (3)	32
Rice Beverages[e]	109 (39)	6 – 320 (39)	60 (42)	1 – 278 (42)	28 (30)	5 – 85 (30)	< LOD	< LOD	42
Rice Wine[e]	19 (22)	5 – 40 (22)	11 (22)	3 – 28 (22)	7 (9)	4 – 12 (9)	< LOD	< LOD	22
Hot/Ready-to-eat Cereal	176 (110)	50 – 810 (110)	100 (110)	20 – 545 (110)	63 (110)	7 – 493 (110)	6 (13)	3 – 14 (13)	110
Infant Cereal[f]	191 (69)	60 – 373 (69)	120 (69)	39 – 254 (69)	77 (69)	15 – 204 (69)	5 (41)	2 – 12 (41)	69
Toddler Cereal[f]	148 (16)	67 – 373 (16)	101 (16)	64 – 180 (16)	58 (16)	24 – 204 (16)	8 (3)	4 – 12 (3)	16
Cookies	77 (43)	30 – 200 (43)	52 (43)	18 – 105 (43)	21 (42)	6 – 92 (42)	11 (2)	5 – 17 (2)	43
Rice Protein Powders	109 (11)	60 – 230 (11)	58 (12)	4 – 152 (12)	16 (9)	6 – 22 (9)	4 (3)	3 – 6 (3)	12
Cereal/Granola Bars	74 (86)	10 – 222 (86)	43 (86)	5 – 127 (86)	23 (80)	1 – 158 (80)	< LOD	< LOD	86
Meal Replacement/ Energy Bars	68 (29)	10 – 130 (29)	50 (29)	5 – 98 (29)	13 (21)	6 – 28 (21)	< LOD	< LOD	29
Infant Formula	1 (8)	1 – 2 (8)	1 (10)	0 – 1 (10)	NS[h]	NS	NS	NS	10
Pasta	206 (23)	149 – 390 (23)	120 (23)	65 – 192 (23)	74 (23)	10 – 133 (23)	< LOD	< LOD	23
Rice Cakes	255 (59)	32 – 620 (59)	145 (59)	23 – 273 (59)	123 (59)	15 – 477 (59)	9 (30)	5 – 17 (30)	59
Savory Rice Snacks	149 (119)	23 – 1931 (119)	73 (119)	15 – 172 (119)	33 (117)	8 – 160 (117)	7 (14)	3 – 21 (14)	119
Sweet Rice Snacks	74 (21)	9 – 127 (21)	34 (22)	1 – 66 (22)	35 (19)	8 – 87 (19)	< LOD	< LOD	22

Note: The FDA samples were composites of six subsamples each; in some cases the sub-samples were taken from six packages with identical lot numbers, in some cases the subsamples were taken from six packages with different lot numbers, and in some cases the subsamples were taken from a single package.

[a] ppb = parts per billion (microgram/kilogram)

[b] n = number of samples used in the calculation

[c] DMA = dimethylarsinic acid

[d] MMA = monomethylarsonic acid
[e] An assumption was made that 1 ml = 1 g for the purposes of calculating inorganic arsenic per serving
[f] The 16 Toddler Cereal samples are a subset of the Infant Cereal category due to potential use in both infants and toddlers
[g] NS = not speciated. All 10 samples were below the threshold for speciation

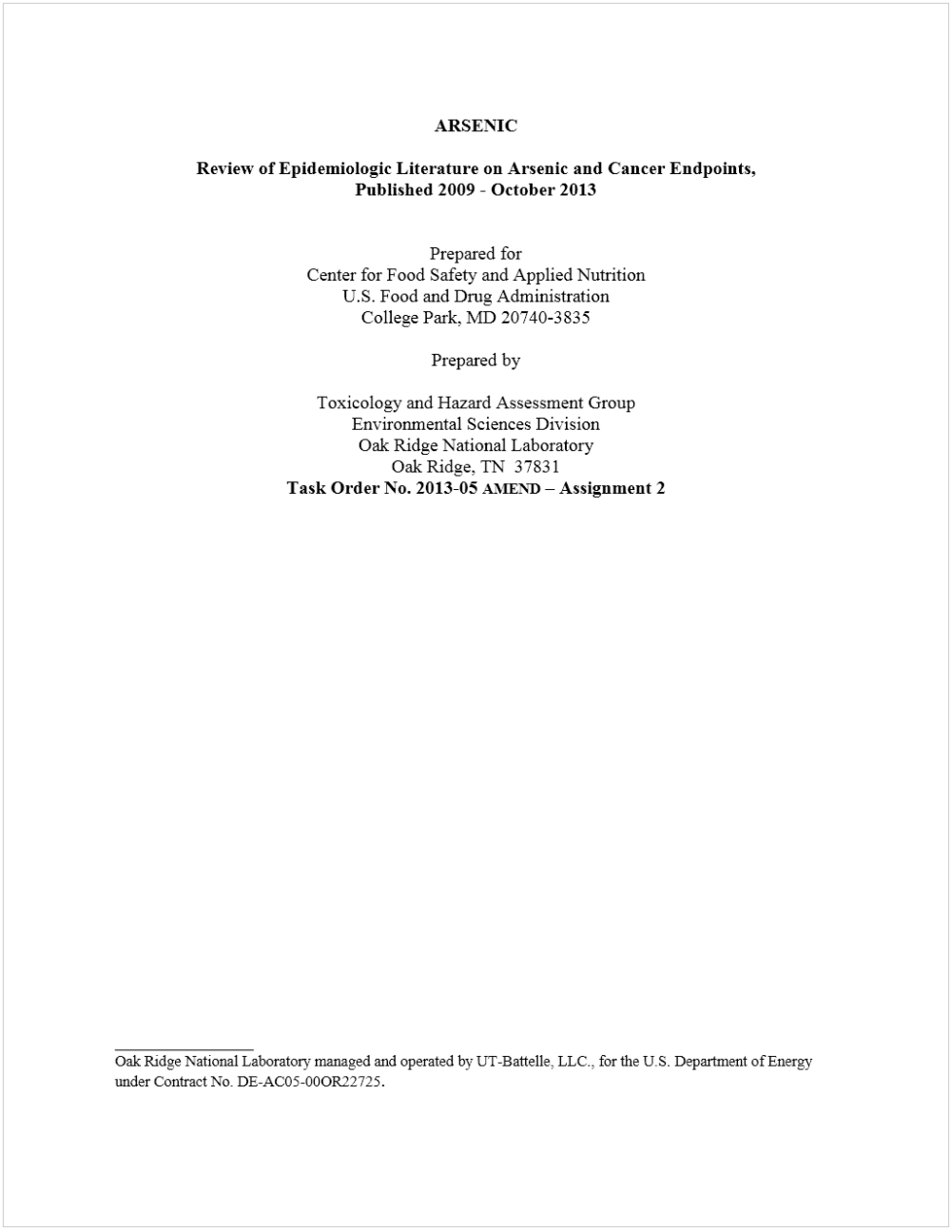
Table 9.15. Summary Table – Arsenic in Infant Rice Cereal (FDA, 2016)

Product Category	Average Total Arsenic ppb[a]	Range of Total Arsenic ppb	Average Inorganic Arsenic ppb	Range of Inorganic Arsenic ppb	Average DMA[b] ppb (n)[c]	Range of DMA ppb (n)	Average MMA[d] ppb (n)	Range of MMA ppb (n)	Total Number of Samples
Cereal – Infant/Toddler	124	18.0 – 224	97.8	20.8 – 126	30.5 (80)	3.3 – 94.2 (80)	4.6 (3)	4.4 – 4.8 (3)	82

[a] ppb = parts per billion (microgram/kilogram)
[b] DMA = dimethylarsinic acid
[c] n = number of samples used in the calculation
[d] MMA = monomethylarsonic acid

9.6 OAK RIDGE LITERATURE REVIEWS

9.6.1 EPIDEMIOLOGY STUDIES REVIEW



ARSENIC

Review of Epidemiologic Literature on Arsenic and Cancer Endpoints, Published 2009 - October 2013

Prepared for
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
College Park, MD 20740-3835

Prepared by

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Environmental Sciences Division
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Oak Ridge, TN 37831
Task Order No. 2013-05 AMEND – Assignment 2

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Figure 9.30a. Oak Ridge National Laboratory (ORNL) Review of Epidemiologic Literature on Arsenic and Cancer Endpoints

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Figure 9.30b. ORNL Review Table of Contents

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Figure 9.30c. ORNL Review List of Tables

Review of Epidemiologic Literature on Arsenic and Cancer Endpoints, Published 2009 - October 2013

I. FDA WORK ASSIGNMENT:

In September, 2013, the U.S. FDA Office of Food Additive Safety sent Work Assignment 2013-05 to ORNL, to provide support for FDA's arsenic and rice risk assessment. The FDA Contact persons listed are Felicia Ellison and Suzanne Fitzpatrick. Work Assignment 2013-05 is a three-part assignment, and the present report addresses Assignment 2, which is reproduced below:

> "Assignment 2. Support for the arsenic dose-response model (for the quantitative cancer risk assessment). Tasks include: (1) Identify experts in consultation with FDA; (2) Conduct a systematic review of the epidemiological literature (select review of papers not evaluated for the 2011 JECFA Monograph 8) on arsenic and cancer endpoints. (3) Apply inclusion/exclusion criteria to identify the data sets to use for dose response modeling.
>
> Note: This work would determine whether the model used for the 2013 FDA Arsenic & apple juice risk assessment needs to be updated/revised. A starting point should be the JEFCA review (Chen studies) and would include a citation forward check of the literature for additional analysis of these data as well as any new studies. This work should be a priority and can begin as soon as a contract is in place."

II. INITIAL STUDY SEARCH: SOURCES AND KEYWORDS:

Three online sources were searched: PubMed (NLM), Toxline (NLM), and the Web of Knowledge (Thomson Reuters).

The search was limited to articles published 2009 to the present (October 2013). The search string used in PubMed and Toxline was "Arsenic AND cancer AND (men OR women OR epidemiol* OR cohort). This yielded 252 results in PubMed; it yielded 459 results in Toxline with PubMed articles included, and 124 articles if PubMed articles were excluded. For the Web of Knowledge, the keywords "arsenic, cancer, and epidemiol*" were searched together, each as a topic, yielding 791 results. Based on an initial screening of each article's title and abstract, a subset of articles from the three searches was selected for more careful examination.

III. STUDY INCLUSION CRITERIA:

A more careful evaluation of the studies obtained from the initial online search (PubMed, Toxline, and the Web of Knowledge) yielded 75 articles that were considered in scope for Assignment 2, per the WA 2013-05 instructions. These articles provided "Support for the arsenic dose-response model for the quantitative cancer risk assessment." The following criteria had to be met for an article to be considered in scope:

Figure 9.30d. ORNL Review: Chapters 1 – 3

(1) The article publication date fell between 2009 and 2013
(2) The article was not included in the JECFA Monograph 8 (2011) Arsenic report
(3) The article described an epidemiological study, or discussed epidemiology studies in which humans were exposed to arsenic
(4) The study evaluated the relationship (dose-response) between exposure to arsenic and cancer or cancer mortality in humans, by oral and/or inhalation exposure. The only non-cancer endpoint evaluated was dermal lesions, because dermal lesions may be precursors or predictors of dermal cancer, and possibly of internal cancers.
(5) Studies that evaluated the effect of human genetic variability, or gene-environment interactions, on arsenic-induced cancer, were only included if the study simultaneously evaluated the relationship between arsenic exposure and cancer. Studies were excluded that evaluated only the relationship between arsenic exposure and the presence of a potential cancer marker (e.g. DNA methylation).

IV. REPORT ORGANIZATION:

The 75 studies that were located in the online searches, and that were considered relevant and useful for fulfilling Assignment 2 of FDA WA 2013-05 were subdivided into four broad categories, consisting of (1) cohort studies (prospective and retrospective); (2) case-control studies; (3) ecological studies; and (4) dermal studies. The dermal studies included cohort, case-control, and ecological studies. The studies in each of these four categories are discussed in a separate report section. Each section includes a table that lists the first author, title, and a summary of the abstract of each study in the respective category. A summary chapter follows, in which 18 of the 75 included studies were selected as good candidates for further dose-response analysis. A listing of the complete references for the 75 included articles concludes this report.

Figure 9.30e. ORNL Review: Chapter 3 – 4

V. COHORT STUDIES (PROSPECTIVE AND RETROSPECTIVE):

Fourteen studies were located that were categorized as prospective or retrospective cohort studies. These varied in their usefulness for an arsenic-cancer dose-response evaluation, the most common shortcoming being poor exposure characterization; confounding by co-exposure to other chemicals was also an issue in several studies. These studies supported the arsenic-cancer dose-response relationship based on the studies of Chen et al. (2010a, 2010b), although none were considered superior, or found an association between arsenic exposure and cancer at a lower drinking water arsenic concentration.

Five of the 14 studies examined the association between occupational (inhalation) exposure to arsenic or arsenic dust and lung cancer. An increased incidence of lung cancer was associated with cumulative exposure to arsenic in tin miners in Yunnan, China, apparently independent of their exposure to radon (Fan et al., 2009; Liu et al., 2013). German uranium miners had an arsenic-related increase in lung squamous cell carcinoma or adenocarcinoma, depending on the presence of concurrent silicosis, and a non-linear increase in stomach cancer, independent of radon exposure (Taeger et al., 2009; Kreuzer et al. 2012). Cumulative exposures to arsenic and cadmium were independently associated with lung cancer mortality in a U.S. cadmium smelter population (Park et al., 2012).

Eight of the cohort studies found a positive association between the levels of arsenic in the drinking water and the incidences of cancer of various internal organs, or of cancer-related mortality. An elevated risk for bladder cancer was found in northern Chile 20 years after controlling arsenic levels in the drinking water (Fernandez et al. 2012). Chung et al. (2013a) found an association between arsenic intake and mortality from cancer of the liver, lung, and bladder in an arseniasis-endemic area of Taiwan. Cancer mortality, heart disease, and all-cause mortality were increased with well-water arsenic exposure in Inner Mongolia, China, for those exposed 10-20 years (Wade et al., 2009). Rahman et al. (2013) found an association between arsenic exposure and death due to cancers and cardiovascular causes combined in children aged 5-18 years Bangladesh. Hsu et al. (2011; 2013) identified several genetic polymorphisms in arsenic methylation enzymes that were associated with an increased risk for arsenic-induced urothelial carcinoma in a Taiwanese population, and determined that diabetic patients had an increased risk for arsenic-induced cancer of the lung, bladder, and kidneys. Liao et al. (2009) used PBPK to model the dose-response data of arsenic-associated bladder, lung, and urinary-related cancers in a Taiwan population exposed long-term to low doses of arsenic; based on the results, a reference guideline drinking water level of 3.4 µg/L was recommended. Arsenic exposure, quantified as the sum of organic and inorganic species in the urine, was associated with mortality due to cancer of the lung, prostate, and pancreas in a U.S. population (Garcia-Esquinas et al. 2013).

No association was found between low levels of dietary arsenic intake (total or inorganic) and cancer risk in a Japanese population, although there was a tendency for increased lung cancer risk in men, which was strengthened by smoking (Sawada et al., 2013).

Summaries of the published abstracts for the cohort studies, as well as the first author and title, are presented in Table 1, where the studies are listed alphabetically by first author.

Figure 9.30f. ORNL Review: Chapter 5 Cohort Studies

TABLE 1. Arsenic and Cancer Endpoints – Cohort Studies 2009-2013

Author, Title; Abstract Summary (listed alphabetically)

Chung et al. 2013a. Urinary arsenic profiles and the risks of cancer mortality: a population-based 20-year follow-up study in arseniasis-endemic areas in Taiwan.
Calculated standardized mortality ratio (SMR) in arseniasis-endemic area of Taiwan from 1996 to 2010. Evaluated relationships between environmental arsenic exposure indices [mg/L As in water] or urinary arsenic profiles and mortality of cause-specific cancer. Collected urine samples and information regarding arsenic exposure from a cohort of 1563 residents. In results, 193 all-site cancer deaths, and 29, 71, 43 deaths respectively for liver, lung and bladder cancers were ascertained. The SMRs were significantly high in arseniasis-endemic areas for liver, lung, and bladder cancers. [From paper: for bladder cancer, OR=7.22 (0.95-55.00) for ≥ 0.71 mg/L As in water]. People with high urinary InAs% or low DMA% or low secondary methylation index (SMI) were the most likely to suffer bladder cancer after adjusting other risk factors. Even after stopping exposure to arsenic from the water, mortality rates were increased.

Fan et al. 2009. Association between sputum atypia and lung cancer risk in an occupational cohort in Yunnan, China.
A prospective cohort study was conducted among occupational tin miners in Yunnan, China in which sputum samples were collected prospectively at baseline and at the following seven annual screenings. Analyzed the association between the incidence of lung cancer and the baseline sputum results or cumulative occupational inhalation exposure. Sputum cytologic atypia was associated with age, smoking, occupational radon and arsenic exposure, and asthma, and was an independent risk factor for lung cancer. [From paper: For occupational arsenic exposure, the incidence ratios from low to high inhalation exposure (Q1 to Q4) were 1.00, 5.83 (95% CI, 3.52 to 9.66), 17.93 (95% CI, 12.13 to 26.49), and 8.88 (95% CI, 5.59 to 14.09), respectively.] For radon exposure, the incidence ratios increased from 1.00 to 10.61 (95% CI, 7.63 to 14.75). Lung cancer risk was higher among men than women and among participants with prior chronic bronchitis or silicosis. [*This study appeared to have evaluated the same cohort, and had results very similar to, that of Liu et al. 2013.*]

Fernández et al. 2012. Long-term impact of arsenic in drinking water on bladder cancer health care and mortality rates 20 years after end of exposure.
Arsenic levels in the drinking water of Northern Chile for the last 60 years were correlated with bladder cancer hospital discharge and mortality rates in recent decades. Bladder cancer hospital discharge rates were higher (peak RR 3.6, 95% CI 3.0-4.7), and mortality rates for bladder cancer showed a trend of increase, reaching peak mortality rates of 28.4 per 100,000 for men and 18.7 per 100,000 for women in the last 10 years. Mortality risk was increased for men (IRR 5.3, 95% CI 4.8-5.8) and women (IRR 7.8, 95% CI 7.0-8.7) and the mean age at cancer specific death was significantly lower in the exposed region (69.6 years, 95% CI 68.4-70.7 vs. 73.7 years, 95% CI 73.3-74.2, p <0.01). Exposure to arsenic was related to bladder cancer and high mortality rates even 20 years after controlling arsenic levels in drinking water.

Garcia-Esquinas et al. 2013. Arsenic Exposure and Cancer Mortality in a US-based Prospective Cohort: the Strong Heart Study.
Evaluated the association between baseline arsenic exposure and cancer mortality in 3,932 American Indians 45-74 years from Arizona, OK and North/South Dakota who participated in the Strong Heart Study in 1989-1991 and were followed through 2008. Inorganic arsenic exposure was sum of inorganic and methylated species in urine. Cancer deaths (386 overall, 78 lung, 34 liver, 18 prostate, 26 kidney, 24 esophagus/stomach, 25 pancreas, 32 colon/rectal, 26 breast, 40 lymphatic/hematopoietic) were assessed by mortality surveillance reviews. Median (interquartile range) urine concentration for inorganic plus methylated arsenic species was 9.7 (5.8-15.6) µg/g creatinine. The adjusted hazard ratios (95% CI) comparing the 80th versus 20th percentiles of arsenic were 1.14 (0.92-1.41) for overall cancer, 1.56 (1.02-2.39) for lung cancer, 1.34 (0.66, 2.72) for liver cancer, 3.30 (1.28-8.48) for prostate cancer, and 0.44 (0.14, 1.14) for kidney cancer. The corresponding hazard ratios were 2.46 (1.09-5.58) for pancreatic cancer, and 0.46 (0.22-0.96) for lymphatic and hematopoietic cancers. Arsenic was not associated with cancers of the esophagus, stomach, colon, rectum, or breast.

Figure 9.30g. ORNL Review: Chapter 5 List of Cohort Studies, Part 1

TABLE 1. Arsenic and Cancer Endpoints – Cohort Studies 2009-2013
Hsu et al. 2011. Genetic polymorphisms in glutathione S-transferase (GST) superfamily and risk of arsenic-induced urothelial carcinoma in residents of southwestern Taiwan. To estimate individual susceptibility to arsenic-induced urothelial carcinoma (UC), 764 DNA specimens from our long-term follow-up cohort in Southwestern Taiwan [established 1988] were used and the genetic polymorphisms in GSTM1, GSTT1, GSTP1 and arsenic methylation enzymes including GSTO1 and GSTO2 were genotyped. The GSTT1 null was marginally associated with increased urothelial carcinoma (UC) risk (HR, 1.91, 95% CI, 1.00-3.65), while the association was not observed for other GSTs. Among the subjects with cumulative arsenic exposure (CAE) ≥ 20 mg/L*year [other group was <20 mg/L*year], the GSTT1 null genotype conferred a significantly increased cancer risk (RR, 3.25, 95% CI, 1.20-8.80). The gene-environment interaction between the GSTT1 and high arsenic exposure with respect to cancer risk was statistically significant. The genetic effects of GSTO1/GSTO2 were largely confined to high arsenic level (CAE ≥ 20).
Hsu et al. 2013a. The association of diabetes mellitus with subsequent internal cancers in the arsenic-exposed area of Taiwan. The southwestern Taiwan cohort had high arsenic levels in their well water, while the northeastern Taiwan cohort had low-to-moderate arsenic levels in their well water. A total of 9525 subjects were recruited. The disease and status of the subjects were ascertained through the Taiwan National Database/Registry. The subjects were followed from study entry (between May 1985 and July 1989) through 2009. Cox regression analysis showed that diabetic patients had a 58% higher risk of any site internal cancer compared to non-DM individuals (HR, 1.58; 95% CI: 1.39–1.79) after adjusting for age, sex, education level, cigarette smoking, alcohol drinking, geographical location, cumulative arsenic exposure and history of hypertension or dyslipidemia. A significant association of DM with cancers of the stomach (HR, 1.75; 95% CI: 1.12–2.76), colon (HR, 1.76; 95% CI: 1.20–2.59), liver (HR, 2.46; 95% CI: 1.81–3.34), pancreas (HR, 2.80; 95% CI: 1.30–6.20) and lungs (HR, 1.35; 95% CI: 1.04–1.76) was observed. The association with lung, bladder and kidney cancer was largely confined to diabetic patients with arsenic level in consumed water ≥500 μg/L, while the association with other cancer sites did not show such an effect.
Kreuzer et al. 2012. Occupational dust and radiation exposure and mortality from stomach cancer among German uranium miners, 1946-2003. The German uranium miner cohort includes 58,677 miners with complete information on occupational exposure to dust, arsenic [dust] and radiation dose based on a detailed job-exposure matrix. A total of 592 stomach cancer deaths occurred in the follow-up period from 1946 to 2003. A Poisson regression model stratified by age and calendar year was used to calculate the excess relative risk (ERR) per unit of cumulative exposure to fine dust or from cumulative absorbed dose to stomach from α or low-LET (low linear energy transfer) radiation. For arsenic exposure, a binary quadratic model was applied [arsenic content in the deposit and the data on inhalable dust exposure were used in the JEM to obtain arsenic exposures because only a few measurements of arsenic levels in air were available]. After adjustment for each of the three other variables, a statistically non-significant linear relationship was observed for absorbed dose from low-LET radiation, α radiation, and fine dust. The relationship between stomach cancer and arsenic exposure was non-linear with a 2.1-fold higher RR (95% CI 0.9 to 3.3) in the exposure category above 500 vs. 0 $\mu g/m^3$ x years (dust-years).
Liao et al. 2009. Risk assessment of arsenic-induced internal cancer at long-term low dose exposure. Linked the Weibull dose-response function and a physiologically based pharmacokinetic (PBPK) model to estimate a reference arsenic guideline. The proposed epidemiological data are based on an 8 years follow-up study of 10,138 residents in arseniasis-endemic areas in southwestern and northeastern Taiwan. The 0.01% and 1% excess lifetime cancer risk based point-of-departure analysis were adopted to quantify the internal cancer risks from arsenic in drinking water. Positive relationships between arsenic exposures and cumulative incidence ratios of bladder, lung, and urinary-related cancers were found using Weibull dose-response model (r^2=0.58-0.89). The result shows that the reference arsenic guideline is recommended to be 3.4 μg/L, based on male bladder cancer with an excess risk of 10^{-4} for a 75-year lifetime exposure. The likelihood of reference arsenic guideline and excess lifetime cancer risk estimates range from 1.9-10.2 μg/L and 2.84 x 10^{-5} to 1.96 x 10^{-4}, respectively, based on the drinking water uptake rates of 1.08-6.52 L/d.

Figure 9.30h. ORNL Review: Chapter 5 List of Cohort Studies, Part 2

TABLE 1. Arsenic and Cancer Endpoints – Cohort Studies 2009-2013
Liu et al. 2013. [A cohort study on risk factors of lung cancer in Yunnan tin miners]. [Chinese] Investigated radon, cigarette use and other risk factors of lung cancer in Yunnan (China) tin miners in a prospective cohort study using multivariate Cox regression model. Increased risk of lung cancer was associated with age at enrollment, tobacco use, prior bronchitis, and cumulative arsenic and radon exposure, while higher education level was associated with decreased lung cancer risk. An inverse effect of radon exposure rate was observed. There was no significant association between lung cancer risk and first radon exposure age. There was a significant additive interaction between tobacco use and radon exposure on lung cancer risk. [*This study appeared to have evaluated the same cohort, and had results very similar to, that presented in Fan et al. 2009, which was in English.]*
Park et al. 2012. Cadmium and lung cancer mortality accounting for simultaneous arsenic exposure. A cadmium smelter [cohort] population [Denver, CO] exhibiting excess lung cancer was re-analysed using a retrospective exposure assessment for arsenic (As), updated mortality (1940-2002), a revised cadmium (Cd) exposure matrix and improved work history information. Cumulative exposure metrics for both cadmium and arsenic [arsenic exposure matrix was based on models predicting air concentrations of As from total dust measurements, feedstock arsenic levels recorded since 1939, and urinary arsenic measurements] were strongly associated making estimation of their independent effects difficult. The results demonstrate (1) a statistically significant effect of Cd independent of As (SMR=3.2 for 10 mg-year/m^3 Cd, p=0.012), (2) a substantial healthy worker effect for lung cancer (for unexposed workers, SMR=0.69) and (3) a large deficit in lung cancer mortality among Hispanic workers (SMR=0.27, p=0.009), known to have low lung cancer rates. [With Cd and As cumulative exposures as linear terms in an additive RR model, each exposure alone was a highly significant predictor of lung cancer mortality.].
Rahman et al. 2013. Increased childhood mortality and arsenic in drinking water in Matlab, Bangladesh: a population-based cohort study. Prospectively assessed whether long-term and recent arsenic exposures are associated with all-cause and cancer and cardiovascular mortalities [combined] in a cohort of 58,406 children aged 5-18 years in Bangladesh and followed during 2003-2010. After adjusting covariates, hazard ratios (HRs) for all-cause childhood deaths comparing lifetime average exposure 10-50.0, 50.1-150.0, 150.1-300.0 and ≥300.1µg/L were 1.37 (95% CI, 0.74-2.57), 1.44 (95% CI, 0.88-2.38), 1.22 (95% CI, 0.75-1.98) and 1.88 (95% CI, 1.14-3.10) respectively. Girls had higher mortality risk compared to boys in relation to baseline exposure. For all cancers and cardiovascular deaths combined, multivariable adjusted HRs amounted to 1.53 (95% CI 0.51-4.57); 1.29 (95% CI 0.43-3.87); 2.18 (95%CI 1.15-4.16) for 10.0-50.0, 50.1-150.0, and ≥150.1 1µg/L, comparing lowest exposure as reference (P for trend=0.009). Adolescents had higher mortality risk compared to children (HRs=1.53, 95% CI 1.03-2.28 vs. HRs=1.30, 95% CI 0.78-2.17).
Sawada et al. 2013. Dietary arsenic intake and subsequent risk of cancer: the Japan Public Health Center-based (JPHC) Prospective Study. The association between arsenic exposure from food (questionnaire data) [Japan restricts arsenic concentration in drinking water to less than 0.01 mg/L] and incidence of cancer was examined in a population-based prospective study in 90,378 Japanese men and women aged 45-74 years. During 11 years of follow-up, 7,002 cancer cases were identified. Hazard ratios (HRs) and 95% CIs for cancer were calculated by Cox proportional hazards modeling. Total arsenic and inorganic arsenic intake showed no association with the risk of total cancer in both men and women, but tended to be associated with an increased risk of lung cancer in men, and were strengthened in currently smoking men. The highest and lowest categories of arsenic and inorganic arsenic intake had HRs (95% CI) of 1.29 (95% CI = 1.03-1.61) and 1.36 (95% CI = 1.09-1.70), respectively. There was an interaction between arsenic and inorganic arsenic intake and smoking status in men (p(interaction) < 0.01 and 0.07, respectively).

Figure 9.30i. ORNL Review: Chapter 5 List of Cohort Studies, Part 3

TABLE 1. Arsenic and Cancer Endpoints – Cohort Studies 2009-2013
Taeger et al. 2009. Major histopathological patterns of lung cancer related to arsenic exposure in German uranium miners. A comprehensive histopathological database and a detailed job-exposure matrix developed for 1,786 former German uranium miners with exposure to arsenic, radon, and quartz were analyzed to assess the effect of arsenic [airborne dust] regarding cell type of lung cancer. Stratification by silicosis was performed. There was an arsenic-related increase of the proportion of squamous cell carcinoma of the lung but restricted to miners without silicosis. The increase was found at all levels of co-exposure to radon and quartz dust. In miners with silicosis, the proportion of adenocarcinoma increased with rising arsenic exposure. Arsenic exposure was associated with non-small cell lung cancer. Silicosis turned out as major determinant of the cell type related with arsenic.
Wade et al. 2009. Increased mortality associated with well-water arsenic exposure in Inner Mongolia, China. Conducted a retrospective mortality study in an Inner Mongolian village exposed to well water contaminated by arsenic since the 1980s. Deaths occurring between January 1, 1997 and December 1, 2004 were classified according to underlying cause and water samples from household wells were tested for total arsenic. Heart disease mortality was associated with arsenic exposure, and the association strengthened with time exposed to the water source. Cancer mortality and all-cause mortality were associated with well-water arsenic exposure among those exposed 10-20 years.
OR = Odds ratio; HR=Hazard ratio

Figure 9.30j. ORNL Review: Chapter 5 List of Cohort Studies, Part 4

VI. CASE-CONTROL STUDIES:

Over 20 studies were located that were considered relevant to evaluating an arsenic-cancer dose-response, and were categorized as case-control studies. Many of the studies evaluated the impact of human genetic variation, such as in arsenic metabolic enzymes, on arsenic-induced cancer. Arsenic exposure was in some studies quantified by measuring its concentration in the drinking water or air, but was in other studies based on levels of arsenic in biomarkers (toenails, urine, blood, or hair). Analysis of urinary arsenic typically measured levels of inorganic arsenic and of its metabolites monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA).

The studies considered most valuable for evaluating the arsenic-cancer dose-response were those in which individual data on exposure to arsenic over a long-term period were available as arsenic levels in drinking water, an adequate number of subjects were included, and the analysis accounted for potential confounders including smoking. Cancers of the renal pelvis and ureter were significantly increased at median arsenic water concentrations ≥300 µg/L (intake of ≥400 µg/day) in a population in northern Chile (Ferreccio et al. 2013). Bladder and lung cancer were significantly increased in subjects from Cordoba, Argentina who drank water containing 91-335 or >335 µg/L arsenic, and non-significant increases were associated with drinking water containing 11-90 µg/L, as compared to water containing <11 µg/L arsenic (Steinmaus et al. 2013). Ever-smokers with high arsenic exposure (≥350 µg/L) had significantly increased risk for bladder cancer and upper urinary tract urothelial carcinoma; the risk of the urothelial carcinoma was increased for carriers of a specific variant of the vascular endothelial growth factor gene (Wang et al. 2012). Conversely, Meliker et al. (2010a; 2010b) found no increase in bladder cancer risk from a lifetime arsenic exposure to drinking water containing 10-100 µg/L arsenic, compared to a reference group exposed to < 1 µg/L in Michigan, U.S. These four case-control studies are consistent with, and support, the arsenic-cancer dose-response relationship based on the studies of Chen et al. (2010a, 2010b). However, a study in subjects from Michigan, U.S. who were exposed to low arsenic concentrations in the drinking water (<50 µg/L), found an increased risk of bladder cancer from drinking water containing >3.72 µg/L for subjects who had particular genetic variant in the arsenic metabolic gene AS3MT (Beebe-Dimmer et al. 2012).

Several occupational exposure case-control studies were published between 2009-3013, in which exposure to arsenic was primarily by inhalation. The risk of sino-nasal squamous cell carcinoma was significantly increased with ever-exposure to arsenic, with a significant increasing trend across ordered cumulative exposure categories, in subjects from the Piedmont region of Italy (d'Errico et al. 2009). A large study in central/eastern Europe and the U.K. that evaluated exposure to 70 occupational agents found that exposure to dust and fumes of arsenic was associated with an increased lung cancer risk ('t-Mannetje et al. 2011). In contrast, Boffetta et al. (2011) found that exposure to arsenic by workers from the Czech Republic, Poland, Romania, and Russia was not associated with an increased risk of renal cell carcinoma, unlike exposure to lead and cadmium.

Biomarkers were used to estimate arsenic exposure in a number of studies, some of which examined the impact of genetic and environmental factors on arsenic-induced cancer. Because levels of arsenic in biological samples reflect relatively recent exposure to arsenic (days to months), these studies are less reliable for predicting the effect of lifetime arsenic exposure. The

Figure 9.30k. ORNL Review: Chapter 6 Case-Control Studies

risk of exocrine pancreatic cancer was increased in subjects from eastern Spain with the highest quartile toenail arsenic (as well as cadmium and lead) concentrations (Amaral et al. 2012). Bladder cancer risk was significantly increased in Tunisian men with high blood arsenic levels, independent of blood cadmium levels, which were associated with smoking and working in the construction industry (Feki-Tounsi et al. 2013a; 2013b). Arsenic concentration in hair and nail samples, as well the incidence of chromosomal aberrations, were higher in residents of West Bengal, India who had blood cancer than in healthy controls (Paul et al. 2011). Bladder cancer risk was increased for subjects in New Hampshire, U.S., who were in the top decile for arsenic exposure, as determined in toenail samples (current levels in drinking water ranged from undetectable to 158 µg/L), and had a number of specific gene variants. These included the double-strand break repair gene XRCC3 T241M, genes for fibrous sheath interacting protein 1, the solute carrier family, and the ZIP family of metal transporters, and various xenobiotic and arsenic-metabolism genes (Andrew et al. 2009; Karagas et al. 2012; Lesseur et al. 2012; Su et al. 2013). An increased risk of urothelial carcinoma was associated with higher levels of urinary arsenic levels (total, inorganic, or MMA), lower plasma alpha-tocopherol levels, and specific variants of the glutathione-S-transferase gene in a Taiwanese population (Chung et al. 2011a; 2011b; 2013b). The risk of renal cell carcinoma increased with levels of urinary arsenic (inorganic, MMA and DMA), the DNA damage marker 8-hydroxydeoxyguanosine, a low glomerular filtration rate, and hypertension in subjects from Taiwan (Huang et al. 2011; 2012). Arsenic-associated lung cancer risk appeared to be increased in subjects who had a high fraction of urinary arsenic as MMA, and who carried a specific variant of the cystathione beta-synthase gene (Steinmaus et al. 2010).

Summaries of the published abstracts for the case-control studies, as well as the first author and title, are presented in Table 2, where the studies are listed alphabetically by first author.

Figure 9.30*l*. ORNL Review: Chapter 6 Case-Control Studies, cont.

TABLE 2. Arsenic and Cancer Endpoints – Case-Control Studies 2009-2013

Author, Title; Abstract Summary (listed alphabetically)

Amaral et al. 2012. Pancreatic cancer risk and levels of trace elements. Evaluated association between trace elements in toenails and risk of exocrine pancreatic cancer (EPC) in 118 EPC cases and 399 hospital controls from eastern Spain. OR and 95% CI, adjusted for potential confounders, were calculated using logistic regression. EPC risk was increased significantly in subjects in the highest quartile concentrations of cadmium (OR 3.58, 95% CI 1.86 to 6.88; $p_{trend}=5\times10^{-6}$), arsenic (OR 2.02, 95% CI 1.08 to 3.78; $p_{trend}=0.009$) and lead (OR 6.26, 95% CI 2.71 to 14.47; $p_{trend}=3\times10^{-5}$). High levels of selenium and nickel were inversely associated with EPC risk.
Andrew et al. 2009. DNA repair genotype interacts with arsenic exposure to increase bladder cancer risk. Study of bladder cancer with XRCC3, ERCC2 genotype/haplotype and arsenic exposure data on 549 controls and 342 cases from New Hampshire. Individual exposure to arsenic was determined in toenail samples. Gene-environment interaction with arsenic exposure was observed in relation to bladder cancer risk for a variant allele of the double-strand break repair gene XRCC3 T241M (adjusted OR 2.8 (1.1-7.3)) comparing to homozygous wild type among those in the top arsenic exposure decile (interaction p-value 0.01). Haplotype analysis confirmed the association of the XRCC3 241.
Beebe-Dimmer et al. 2012. Genetic variation in glutathione S-transferase omega-1, arsenic methyltransferase and methylene-tetrahydrofolate reductase, arsenic exposure and bladder cancer: a case-control study. Examined association between arsenic metabolic genes GSTO-1, As3MT and MTHFR and bladder cancer. Single nucleotide polymorphisms (SNPs) were genotyped in DNA from 219 bladder cancer cases and 273 controls in Southeastern Michigan, exposed to low to moderate (<50 µg/L) levels of arsenic in drinking water. A time-weighted measure of arsenic exposure was constructed from household water samples and merged with arsenic data from multiple sources. While no single SNP in As3MT was significantly associated with bladder cancer overall, those exposed to higher arsenic levels with one or more copies of the C allele in rs11191439 (the Met287Thr polymorphism) had an elevated risk of bladder cancer (OR = 1.17; 95% CI = 1.04-1.32 per 1 µg/L increase in average exposure). Bladder cancer cases were also 60% less likely to be homozygotes for the A allele in rs1476413 in MTHFR compared to controls (OR = 0.40; 95% CI = 0.18-0.88).
Boffetta et al. 2011. Occupational exposure to arsenic, cadmium, chromium, lead and nickel, and renal cell carcinoma: a case-control study from Central and Eastern Europe. The risk of renal cell carcinoma (RCC) in Central and Eastern Europe was investigated in relation to exposure to carcinogenic metals. Methods During 1999-2003, conducted a hospital-based study in Czech Republic, Poland, Romania and Russia, including 1097 cases of RCC and 1476 controls. Occupational exposure to arsenic, cadmium, chromium(III), chromium(VI), lead and nickel was based on occupational questionnaires. The ORs for RCC were 1.55 (95% CI 1.09 to 2.21) for exposure to lead and 1.40 (95% CI 0.69 to 2.85) for exposure to cadmium. Exposure to other metals, including arsenic, did not entail an increased risk of RCC.
Chung et al. 2011a. Protective effects of plasma alpha-tocopherols on the risk of inorganic arsenic-related urothelial carcinoma. A case-control study (in Taiwan) evaluated relationship among the indices of oxidative stress, such as urinary 8-hydroxydeoxyquanine (8-OHdG), as well as plasma micronutrients and urinary arsenic profiles on urothelial carcinoma (UC) risk. There was significant protective effect of plasma alpha-tocopherol on UC risk. Plasma alpha-tocopherol levels were significantly inversely related to urinary total arsenic concentrations and inorganic arsenic percentage (InAs%), and significantly positively related to %DMA. There were no correlations between plasma micronutrients and urinary 8-OHdG. Study participants with lower alpha-tocopherol and higher urinary total arsenic, higher InAs%, higher MMA%, and lower DMA% had a higher UC risk than those with higher alpha-tocopherol and lower urinary total arsenic, lower InAs%, lower MMA%, and higher DMA%.

Figure 9.30m. ORNL Review: Chapter 6 List of Case-Control Studies, Part 1

TABLE 2. Arsenic and Cancer Endpoints – Case-Control Studies 2009-2013
Chung et al. 2011b. Gene polymorphisms of glutathione S-transferase omega 1 and 2, urinary arsenic methylation profile and urothelial carcinoma. Evaluated roles of glutathione S-transferase omega 1 (GSTO1) and GSTO2 polymorphisms in UC carcinogenesis in a hospital-based case-control study. Questionnaire and biological specimens were collected from 149 UC cases and 251 healthy controls in a non-obvious inorganic arsenic exposure area in Taipei, Taiwan. A significant positive association was found between total arsenic, inorganic arsenic percentage and %MMA and UC, while %DMA was significantly inversely associated with UC. The minor allele frequency of GSTO1 Ala140Asp, GSTO1 Glu208Lys and GSTO2 Asn142Asp was 18%, 1% and 26%, respectively. A significantly higher MMA% was found in people who carried the wild type of GSTO1 140 Ala/Ala compared to those who carried the GSTO1 140 Ala/Asp and Asp/Asp genotype (p=0.02). The homogenous variant genotype of GSTO2 142 Asp/Asp was inversely associated with UC risk (OR=0.17; 95% CI, 0.03 - 0.88; p=0.03).
Chung et al. 2013b. The effect of cigarette smoke and arsenic exposure on urothelial carcinoma risk is modified by glutathione S-transferase M1 gene null genotype. Evaluated role of gene-environment interaction in the carcinogenesis of urothelial carcinoma (UC) in a hospital-based case-control study. Information about cigarette smoking exposure was acquired from a lifestyle questionnaire. Multivariate logistic regression showed that UC patients had higher urinary levels of total arsenic, higher percentages of inorganic arsenic (InAs%) and MMA% and DMA% compared to controls. Subjects carrying the GSTM1 null genotype had significantly increased UC risk. No association was observed between gene polymorphisms of CYP1A1, EPHX1, SULT1A1 and GSTT1 and UC risk after adjustment for age and sex.
d'Errico et al. 2009. A case-control study on occupational risk factors for sino-nasal cancer. Investigated risk of sino-nasal epithelial cancer (SNEC) by histological type with cumulative exposure to suspected occupational risk factors in Italy between 1996 and 2000. A questionnaire completed by 113 cases and 336 hospital controls, was used to assign exposure to occupational hazards. Analysis used unconditional logistic regression to statistically adjust for age, sex, smoking and co-exposures, allowing for a 10-year latency period. The risk of adenocarcinoma was significantly increased with ever-exposure to wood dust, leather dust, organic solvents; ever-exposure to welding fumes and arsenic (OR = 4.4) significantly increased the risk for squamous cell carcinoma. A significant increasing trend in risk across ordered cumulative exposure categories was found and, except for arsenic, a significantly increased risk with ever-exposure at low intensity.
Feki-Tounsi et al. 2013a. Low-level arsenic exposure is associated with bladder cancer risk and cigarette smoking: a case-control study among men in Tunisia. Blood samples were analyzed for arsenic concentration to determine a possible association with bladder cancer risk in 124 male bladder cancer cases and 220 controls in Tunisia. The study subjects were stratified into two median groups based on concentrations of arsenic in their blood. Blood arsenic (B-As) was significantly (two to threefold) higher in bladder cancer cases than in controls ($p<0.05$). The arsenic concentrations were significantly higher among both smokers and workers in construction. The adjusted risk ratios for B-As concentration categories 0.1-0.67 and $\geq$ 0.67 µg/L were 0.18 (95% CI=0.014-2.95) and 2.44 (95% CI=1.11-5.35), respectively. Arsenic levels were not found to be associated with tumor grade or stage.
Feki-Tounsi et al. 2013b. Cadmium in blood of Tunisian men and risk of bladder cancer: interactions with arsenic exposure and smoking. A case-control study of Tunisian men [Feki-Tounsi et al. 2013a] was re-examined to assess the levels of cadmium in blood and reparse the association between the simultaneous exposure to cadmium and arsenic, and bladder cancer risk. Levels of blood Cd were significantly twice higher among cases than in controls ($P < 0.05$) and were positively correlated with smoking and age. Additionally, analysis of metal levels among non-smokers showed very high blood Cd and As levels for the coastal regions of Sfax and central Tunisia. After controlling for potential confounders, for low blood As levels (<0.67 µg/L), the OR for blood Cd was 4.10 (95 % CI 1.64-10.81), while for higher As levels (>0.67 µg/L), it was reduced to 2.10 (CI, 1.06-4.17). Adjustment for Cd exposure did not alter the risk associated to As exposure.

Figure 9.30n. ORNL Review: Chapter 6 List of Case-Control Studies, Part 2

TABLE 2. Arsenic and Cancer Endpoints – Case-Control Studies 2009-2013
Ferreccio et al. 2013. Case-control study of arsenic in drinking water and kidney cancer in uniquely exposed northern Chile. Performed a case-control study in 2007-2010 of 122 kidney cancer cases and 640 population-based controls with individual data on exposure and potential confounders northern Chile. Cases included 76 renal cell, 24 transitional cell renal pelvis and ureter, and 22 other kidney cancers. For renal pelvis and ureter cancers, the adjusted odds ratios by average arsenic intakes of <400, 400-1,000, and >1,000 µg/day (median water concentrations of 60, 300, and 860 µg/L) were 1.00, 5.71 (95% confidence interval: 1.65, 19.82), and 11.09 (95% confidence interval: 3.60, 34.16) (P_{trend} < 0.001), respectively. Odds ratios were not elevated for renal cell cancer. These findings show that drinking-water arsenic causes renal pelvis and ureter cancer in humans.
Huang et al. 2011. Effect of urinary total arsenic level and estimated glomerular filtration rate on the risk of renal cell carcinoma in a low arsenic exposure area. The case-control study was conducted between November 2006 and May 2009 with 132 patients [in Taiwan] with renal cell carcinoma, and 260 sex and age matched controls from a hospital based pool. Urinary arsenic species determined included inorganic arsenic, MMA and DMA. Urinary total arsenic was significantly associated with renal cell carcinoma risk in a dose-response relationship after multivariate adjustment. Low estimated glomerular filtration rate or hypertension was significantly related to renal cell carcinoma risk. Estimated glomerular filtration rate was significantly negatively related with urinary total arsenic. A significant interaction was seen between the urinary total arsenic and hypertension on renal cell carcinoma risk. The greatest odds ratio (6.01) was seen in the subjects with hypertension, low estimated glomerular filtration rate and high urinary total arsenic. A trend test indicated that the risk of renal cell carcinoma increased along with the accumulating number of these three risk factors (p <0.0001).
Huang et al. 2012. Urinary total arsenic and 8-hydroxydeoxyguanosine are associated with renal cell carcinoma in an area without obvious arsenic exposure. 8-Hydroxydeoxyguanosine (8-OHdG) is one of the most reliable and abundant markers of DNA damage. The study was designed to explore the relationship between urinary 8-OHdG and renal cell carcinoma (RCC) and to investigate whether individuals with a high level of 8-OHdG would have a modified odds ratio (OR) of arsenic-related RCC. This case-control study was conducted with 132 RCC patients and 245 age- and sex-matched hospital control patients [in Taiwan] between November 2006 and May 2009. Concentrations of urinary arsenic species were determined. Level of urinary 8-OHdG was significantly associated with the OR of RCC with a dose-response after multivariate adjustment. Urinary 8-OHdG was significantly related to urinary total arsenic. The greatest OR (3.50) was seen in individuals with high urinary 8-OHdG and high urinary total arsenic. A trend test indicated that the OR of RCC was increased with one of these factors and was further increased with both (p=0.002), but the interaction was statistically insignificant.
Karagas et al. 2012. SLC39A2 and FSIP1 polymorphisms as potential modifiers of arsenic-related bladder cancer. To identify variants that may influence risk of arsenic-associated bladder cancer, a subset of bladder cancer cases was screened using ~10,000 non-synonymous single nucleotide polymorphisms (SNPs). Top ranking hits on the SNP array were further analyzed in a population-based case-control study (n = 832 cases and 1,191 controls). SNPs in the fibrous sheath interacting protein 1 (FSIP1) gene (rs10152640) and the solute carrier family 39, member 2 (SLC39A2) in the ZIP gene family of metal transporters (rs2234636) were detected as potential hits in the initial scan and validated in the full case-control study. The adjusted OR for the FSIP1 polymorphism was 2.57 [95% CI 1.13, 5.85] for heterozygote variants (AG) and 12.20 (95% CI 2.51, 59.30) for homozygote variants (GG) compared to homozygote wild types (AA) in the high arsenic group (>90th percentile), and unrelated in the low arsenic group (≤ 90th percentile) (P for interaction = 0.002). For the SLC39A2 polymorphism, the adjusted ORs were 2.96 (95% CI 1.23, 7.15) and 2.91 (95% CI 1.00, 8.52) for heterozygote (TC) and homozygote (CC) variants compared to homozygote wild types (TT), respectively, and close to one in the low arsenic group (P for interaction = 0.03).

Figure 9.30*o*. ORNL Review: Chapter 6 List of Case-Control Studies, Part 3

TABLE 2. Arsenic and Cancer Endpoints – Case-Control Studies 2009-2013
Lesseur et al. 2012. A case-control study of polymorphisms in xenobiotic and arsenic metabolism genes and arsenic-related bladder cancer in New Hampshire. Investigated gene-environment interactions between arsenic metabolic gene polymorphisms and arsenic exposure in relation to bladder cancer risk with a population-based case-control study in New Hampshire (832 cases and 1191 controls). Toenail arsenic concentrations were used to classify subjects into low and high exposure groups. Single nucleotide polymorphisms (SNPs) in GSTP1, GSTO2, GSTZ1, AQP3, AS3MT and the deletion status of GSTM1 and GSTT1 were determined. There was evidence of genotype-arsenic interactions in the high exposure group; GSTP1 Ile105Val homozygous individuals had an OR of 5.4 [95% CI: 1.5-20.2; P for interaction=0.03] and AQP3 Phe130Phe carriers had an OR=2.2 (95% CI: 0.8-6.1; P for interaction=0.10). Bladder cancer risk overall was associated with GSTO2 Asn142Asp and GSTZ1 Glu32Lys.
Meliker et al. 2010a. Lifetime exposure to arsenic in drinking water and bladder cancer: a population-based case-control study in Michigan, USA. This population-based case-control study in southeastern Michigan, USA included 411 bladder cancer cases diagnosed between 2000 and 2004, and 566 controls recruited during the same period, which were exposed to 10-100 µg/L arsenic. Individual lifetime exposure profiles were reconstructed, and residential water source histories, water consumption practices, and water arsenic measurements or modeled estimates were determined at all residences. Arsenic exposure was estimated for 99% of participants' person-years. Overall, an increase in bladder cancer risk was not found for time-weighted average lifetime arsenic exposure >10 µg/L when compared with a reference group exposed to <1 µg/L (OR = 1.10; 95% CI: 0.65, 1.86). Among ever-smokers, risks from arsenic exposure >10 µg/L were similarly not elevated when compared to the reference group (OR = 0.94; 95% CI: 0.50, 1.78).
Meliker et al. 2010b. Incorporating individual-level distributions of exposure error in epidemiologic analyses: an example using arsenic in drinking water and bladder cancer. Quantitative estimates of exposure and its associated error were used to create for each individual a normal distribution of exposure estimates which was then sampled using Monte Carlo simulation. Then, the relationship between exposure and disease is evaluated 99 times generating a distribution of risk estimates and confidence intervals. This is demonstrated in a bladder cancer case-control study using individual-level distributions of exposure to arsenic in drinking water. Sensitivity analyses indicated similar performance for categorical or continuous exposure estimates, and that increases in exposure error translate into a wider range of risk estimates. Bladder cancer analyses yield a wide range of possible risk estimates, allowing quantification of exposure error in the association between arsenic and bladder cancer, typically ignored in conventional analyses.
Paul et al. 2011. Association of genotoxic effects of arsenic with haematological malignancy in West Bengal. Investigated whether arsenic plays any role in the increased incidence of blood cancer among residents of West Bengal, India. The study group included blood cancer patients and age-, sex-matched healthy controls [case-control]. Arsenic concentration was measured in the hair and nail samples. Found significantly higher arsenic concentration in the biological tissues of patients, which also correlated with their greater incidence of chromosomal aberrations. Thus, arsenic may act as a predisposing factor for blood cancer.
Steinmaus et al. 2010. Individual differences in arsenic metabolism and lung cancer in a case-control study in Cordoba, Argentina. Human urinary arsenic metabolites were assessed in 45 lung cancer cases and 75 controls from arsenic-exposed areas in Cordoba, Argentina. Folate has also been linked to arsenic-disease susceptibility, thus associations between single nucleotide polymorphisms in folate metabolizing genes, arsenic methylation, and lung cancer was also evaluated. In analyses limited to subjects with metabolite concentrations above detection limits, the mean %MMA was higher in cases than in controls (17.5% versus 14.3%, p=0.01). The lung cancer odds ratio for subjects with %MMA in the upper tertile compared to those in the lowest tertile was 3.09 (95% CI, 1.08-8.81). Although the study size was too small for a definitive conclusion, there was an indication that lung cancer risks might be highest in those with a high %MMA who also carried cystathionine beta-synthase (CBS) rs234709 and rs4920037 variant alleles.

Figure 9.30p. ORNL Review: Chapter 6 List of Case-Control Studies, Part 4

TABLE 2. Arsenic and Cancer Endpoints – Case-Control Studies 2009-2013
Steinmaus et al. 2013. Drinking water arsenic in northern Chile: high cancer risks 40 years after exposure cessation. In Antofagasta, Chile, >250,000 people were exposed to high arsenic drinking water concentrations from 1958 until 1970, when a water treatment plant was installed. Because of its unique geology, limited water sources, and good historical records, lifetime exposure and long-term latency patterns can be accurately assessed in this area. Conducted a population-based case-control study from October 2007 to December 2010 involving 232 bladder and 306 lung cancer cases and 640 age- and gender-matched controls, with detailed information on past exposure and potential confounders, including smoking and occupation. Bladder cancer ORs for quartiles of average arsenic concentrations in water before 1971 (<11, 11-90, 91-335, and >335 µg/L) were 1.00, 1.36 [95% CI, 0.78-2.37], 3.87 (2.25-6.64), and 6.50 (3.69-11.43), respectively. Corresponding lung cancer ORs were 1.00, 1.27 (0.81-1.98), 2.00 (1.24-3.24), and 4.32 (2.60-7.17). Bladder and lung cancer ORs in those highly exposed during 1958 to 1970 but not thereafter were 6.88 (3.84-12.32) and 4.35 (2.57-7.36), respectively.
Su et al. 2013. Using Bayesian networks to discover relations between genes, environment, and disease. The Bayesian network was applied to assess interactions between DNA repair genes and arsenic exposure [toenail arsenic high/low] in increasing bladder cancer risk in a population-based case-control study of bladder cancer in New Hampshire, USA (Andrew et al., 2009). Assessing polymorphisms in the XRCC3 and ERCC2/XPD genes using logistic regression, evidence of an increased risk of bladder cancer among those in the top arsenic exposure decile was observed for those with a variant allele of the double-strand break repair gene XRCC3.
't-Mannetje et al. 2011. Occupational exposure to metal compounds and lung cancer. Results from a multi-center case-control study in Central/Eastern Europe and UK. A population-based lung cancer case-control study in Central/Eastern Europe and UK was conducted in 1998-2003, including 2,853 cases and 3,104 controls. Exposure to 70 occupational agents was assessed. Odds ratios (OR) for exposure to dust and fumes/mist of chromium, nickel, cadmium, arsenic, as well as inorganic pigment dust and inorganic acid mist, were adjusting for smoking, age, center, sex, and exposure to other occupational agents including the metals. Exposure to arsenic (prevalence = 1.4%) was associated with an increased lung cancer risk (OR 1.65, 95% CI: 1.05-2.58). [Arsenic exposure was not quantified but was estimated based on occupation.] For chromium dust, a linear upward trend for duration and cumulative exposure was observed. A weak association was observed for exposure to cadmium fumes. No increased risk was observed for inorganic acid mist, inorganic pigment dust, or nickel.
Wang et al. 2012. Comparing the joint effect of arsenic exposure, cigarette smoking and risk genotypes of vascular endothelial growth factor on upper urinary tract urothelial carcinoma and bladder cancer. Investigated the joint effect of arsenic exposure, cigarette smoking, and vascular endothelial growth factor (VEGF) polymorphisms on risk of urothelial carcinoma (UC) in a hospital-based case-control study consisting of 470 bladder cancers, 260 upper urinary tract UCs (UUTUCs), and 850 age-matched controls, recruited from September 1998 to December 2009. UC risk was estimated by ORs and 95% confidence intervals using unconditional logistic regression. Ever smokers with high arsenic exposure had significantly increased risks of 5.7 and 6.4 for bladder cancer and UUTUC, respectively. Ever smokers with high arsenic exposure carrying 1 or 2 risk genotypes of the VEGF gene had a significantly increased risk of 6.6 for bladder cancer and 9.9 for UUTUC, and UUTUC cases with high arsenic exposure carrying 1 or 2 risk genotypes of the VEGF gene had a non-significant increased risk of advanced tumor stage. Thus arsenic exposure, cigarette smoking, and risk genotypes of VEGF contribute to a higher risk of UUTUC than of bladder cancer.
OR = Odds ratio; MMA =monomethylarsonic acid; DMA=dimethylarsinic acid

Figure 9.30q. ORNL Review: Chapter 6 List of Case-Control Studies, Part 5

VII. ECOLCOGICAL STUDIES:

Approximately 20 studies were located that were considered relevant to evaluating an arsenic-cancer dose-response, and were categorized as ecological studies. An ecological study is defined as an epidemiological study in which the unit of analysis is a population, typically in a specific geographic region, rather than an individual. Ecological studies are often considered inferior to non-ecological studies (e.g., cohort and case-control) because they are subject to the "ecological fallacy," in which individuals' responses are assumed to be the same as the response of the group to which those individuals belong. A lack of sensitivity is another common shortcoming of ecological studies; of the 19 studies presented below, four found no association between arsenic exposure and incidence of cancer or cancer mortality. Ecological studies can be quite valuable and informative, however, if detailed arsenic exposure information is available. In the located studies, arsenic exposure was most often quantified by measuring its concentration in drinking water, although several studies based exposure on arsenic levels in toenail samples, air, soil, stream sediment, or lichens.

The most notable study, in terms of potentially having an impact on the arsenic-cancer dose-response assessment, was one conducted in Córdoba, Argentina by Pou et al. (2011). Statistically significant increases in mortality due to bladder cancer occurred in males and/or females from consumption of drinking water containing inorganic arsenic levels of 0-40 µg/L (RR=3.14 for males); 40-320 µg/L (RR=4.03 for males); and 320-1800 µg/L (RR=4.71 for males, 1.22 for females), when compared to the female low exposure group. The incidence of bladder cancer mortality decreased from 1986-2006 in both sexes, along with a decrease in water arsenic levels. This study suggests that water arsenic levels below 40 µg/L might cause cancer, which contradicts the findings of a number of cohort and case control studies. In a review of this study, however, Cohen et al. (2013) asserted that the results were highly equivocal because bladder cancer rates for highly exposed men were compared with rates for low exposed women and not men, lung cancer mortality was used as a surrogate for smoking status, and the reduction in overall bladder cancer mortality over time did not address factors such as improved medical care and decreased smoking incidence.

Three other ecological studies were conducted in Argentina. Aballay et al. (2012) found an association between arsenic distribution in groundwater supplies in Córdoba, and geographic patterns of age-standardized incidence rates of colon cancer in women, and lung and bladder cancers in men and women. Mortality from kidney, lung, liver, and skin cancer was associated with the distribution of arsenic in groundwater in different hydrogeological regions in the Cordoba Province, although risk factors such as smoking, pollution, and ultraviolet ray exposure were not taken into account (Francisca and Carro Perez, 2009). High water arsenic concentration (range was 0.3 to 187 mg/L), poverty, and a lack of potable water were associated with a 2 to 4-fold greater risk of death from tumors of the respiratory tract and urinary tract in Buenos Aires (Navoni et al. 2012).

Five ecological studies were conducted in Taiwan, of which three found a correlation between arsenic exposure and cancer. A significant positive association was found between intake of drinking water containing >0.64 mg/L arsenic (but not ≤0.64 mg/L) and bladder cancer incidence in men and women, using three methods of age adjustment (direct, indirect, and variable) (Guo,

Figure 9.30r. ORNL Review: Chapter 7 Ecological Studies

2011). Arsenic drinking water levels >0.64 mg/L were associated with an increase in liver cancer mortality in men and women, after adjusting for age, in 138 southwestern villages (Lin et al. 2013). The incidence rate of oral cancer was geographically related to the concentrations of arsenic (and nickel, independently) in farm soil in the cancer patients' residential areas, after controlling for cigarette smoking and betel quid chewing (Su et al. 2010). In contrast, no dose-response was found between soil arsenic levels and lung cancer incidence in Taiwan, using a geographical information system to plot the maps of soil heavy metal concentration and lung cancer incidence rates; associations were found for chromium, copper, mercury, nickel, and zinc (Huang et al. 2013). A significant negative association was found for bladder and lung cancer deaths relative to arsenic exposure (µg/kg/day) for a group of villages with water arsenic levels <150 µg/L; a positive association was only found by assuming zero arsenic exposure from drinking water for the comparison population (Lamm et al 2013).

Three of the four ecological studies conducted in the U.S. found an association between arsenic exposure and cancer. Residents of 23 rural Kentucky counties had higher concentrations of arsenic, chromium, and nickel in toenail clippings, and higher lung cancer incidence and colorectal mortality rates than residents from an urban Kentucky county (Johnson et al., 2011). Spatial modeling determined that clusters of persons diagnosed with pancreatic cancer or with bladder cancer were more likely to be located near arsenic-contaminated drinking water wells in Florida (Nieder et al. 2009; Liu-Mares et al. 2013). Levels of arsenic stream sediment were associated with an increase in the incidence of lung cancer in 742 counties, after controlling for smoking and income; a significant interaction existed between arsenic exposure and smoking prevalence (Putila and Guo. 2011). However, no association was found between industrial air and water releases of arsenic in 215 counties, as obtained from the Toxics Release Inventory (TRI), and age-adjusted lung cancer incidence from the Surveillance, Epidemiology, and End Results (SEER) database, although such associations were found for chromium, formaldehyde, and nickel (Luo et al. 2011).

Ecological studies were also conducted in several other countries. Atmospheric deposition of arsenic, as measured by lichen biomonitoring, was associated with child mortality due to leukemia in a Portuguese population, using Bayesian hierarchical modeling (Martinho and Freitas 2009). Analysis of Cancer Registry and geochemical data in the gold mining region of Victoria, Australia showed an association between soil arsenic levels and the incidence of all cancers, and of melanoma in more socioeconomically disadvantaged areas (Pearce et al. 2012). An increased rate of mortality from bladder cancer, laryngeal cancer, liver cancer, and chronic renal disease in adults <50 years of age resulted from *in utero* and childhood exposure to high arsenic concentrations in drinking water (870 µg/L) in Antofagasta, Chile (Smith et al. 2012). Birth cohorts in western Japan (Okayama Prefecture) that drank arsenic-contaminated milk powder during early summer in 1955 had increased cancer mortality (total, liver, pancreatic, and hematopoietic cancers, but not lung or bladder/kidney) (Yorifuji et al. 2011). Conversely, a statistically significant trend was not found between mortality or cancer incidence and soil arsenic levels in municipalities in rural Slovakia (Gulis et al. 2009).

Summaries of the published abstracts for the ecological studies, as well as the first author and title, are presented in Table 3, where the studies are listed alphabetically by first author.

Figure 9.30s. ORNL Review: Chapter 7 Ecological Studies, cont.

TABLE 3. Arsenic and Cancer Endpoints – Ecological Studies 2009-2013

Author, Title; Abstract Summary (listed alphabetically)

Aballay et al. 2012. Cancer incidence and pattern of arsenic concentration in drinking water wells in Córdoba, Argentina.
Evaluated association between geographic patterns of cancer incidence and the distribution of As in groundwater supplies. Age standardized incidence rates (ASIRs) were obtained from Córdoba (Argentina) Cancer Registry (CCR), and As data from official reports of monitoring wells (aquifers). A multilevel model was applied. Total ASIRs by aquifers for males/females were 191.01/249.22 (Rioja plain); 215.03/225.37 (Pampa hills); and 239.42/188.93 (Chaco-Pampa plain). As was associated with increased risk of colon cancer in women, and lung and bladder cancers in both sexes. It had no association with breast cancer

Francisca and Carro Perez. 2009. Assessment of natural arsenic in groundwater in Cordoba Province, Argentina.
Analyzed the spatial distribution of arsenic in different hydrogeological regions in the Cordoba Province of Argentina, to define the naturally expected concentration in an aquifer, and identified data related to cancer mortality in the study area. The correlation between arsenic and fluoride concentrations in groundwater is analyzed at each county. The results show that the Chaco-Pampean plain hydrogeologic region is the most affected area, with arsenic and fluoride concentrations in groundwater being generally higher than the values suggested by the World Health Organization (WHO) for drinking water. Mortality related to kidney, lung, liver, and skin cancer in this area could be associated to the ingestion of arsenic-contaminated water.

Gulis et al. 2009. Natural and man-made health hazards in rural Slovakia.
Observational (ecological) study design was employed to study rural gardening practices and their impact on health. Statistically significant differences in SIR were found in rural areas of Spis-Gemer Region (SGR) among males for lip, oral cavity and larynx (1.60, CI 95% 1.12-2.34), respiratory (1.25, CI 95% 1.01-1.55) and digestive organ cancers (1.22, CI 95% 1.01-1.47); hematopoietic cancers are significantly elevated among males in rural areas as well (1.58, CI 95% 1.05-2.39). Study shows that on ecological level, mortality and morbidity statistics could be used to assess human health status in linkage to broad exposure measures (urban-rural); on dose response level (arsenic in soil) this method lacks sensitivity [no statistically significant trend was identified in mortality or in incidence of cancer due to changing arsenic concentration levels in the municipalities].

Guo HR. 2011. Age adjustment in ecological studies: using a study on arsenic ingestion and bladder cancer as an example.
Compared three methods of age adjustment in a study on the associations between arsenic in drinking water and incidence of bladder cancer in Taiwan. A total of 3068 cases of bladder cancer, including 2276 men and 792 women, were identified during a ten-year study period. In the regression analysis, the first method (Direct) applied direct standardization to obtain standardized incidence rate and then used it as the dependent variable. The second (Indirect Method) applied indirect standardization to obtain standardized incidence ratio and then used it as the dependent variable in the regression analysis instead. The third (Variable Method) used proportions of residents in different age groups as a part of the independent variables in the multiple regression models. All three methods showed a significant positive association between arsenic exposure >0.64 mg/L and incidence of bladder cancer in men and women, but different results were observed.

Huang et al. 2013. Cell-type specificity of lung cancer associated with low-dose soil heavy metal contamination in Taiwan: an ecological study.
Calculated the annual averages of eight soil heavy metals (i.e., As, Cd, Cr, Cu, Hg, Ni, Pb, and Zn) in Taiwan from 1982 to 1986. The age-standardized incidence rates of lung cancer (adenocarcinoma [AC] and squamous cell carcinoma [SCC]) in Taiwan were obtained from 2001 to 2005. A geographical information system was used to plot the maps of soil heavy metal concentration and lung cancer incidence rates. For males, the trend test for lung SCC incidence caused by exposure to Cr, Cu, Hg, Ni, and Zn showed a statistically significant dose-response relationship. However, for lung AC, only Cu and Ni had a significant dose-response relationship. Females achieving a significant dose-response relationship for the trend test were Cr ($P = 0.02$), Ni ($P = 0.02$), and Zn ($P = 0.02$) for lung SCC, and Cu ($P < 0.01$) and Zn ($P = 0.02$) for lung AC. [Little correlation was observed between As and the other seven heavy metals ($r = -0.17–0.18$), and there was no dose-response between As soil levels and lung cancer incidence.]

Figure 9.30t. ORNL Review: Chapter 7 List of Ecological Studies, Part 1

TABLE 3. Arsenic and Cancer Endpoints – Ecological Studies 2009-2013
Johnson et al. 2011. Concentrations of arsenic, chromium, and nickel in toenail samples from Appalachian Kentucky residents. Compared biological exposure to As, Cr, and Ni, and lung and colon cancer rates, demographics, and smoking prevalence, for adults living in Appalachian Kentucky with residents of Jefferson, a non-Appalachian, urban county. Toenail clipping analysis measured As, Cr, and Ni for residents of 23 rural Appalachian Kentucky counties and for Jefferson County. Reverse Kaplan-Meier statistical methodology addressed left-censored data. Appalachian residents were exposed to higher concentrations of As, Cr, and Ni, and had higher lung cancer incidence and colorectal mortality rates than Jefferson County residents.
Lamm et al. 2013. Bladder/lung cancer mortality in Blackfoot-disease (BFD)-endemic area villages with low (<150 µg/L) well water arsenic levels--an exploration of the dose-response Poisson analysis. Poisson analyses was conducted for bladder and lung cancer deaths with respect to arsenic exposure (µg/kg/day) for low-dose (<150 µg/L) Taiwan villages [from study Wu et al., 1989]. Exposure was defined by the village well water median, mean, or maximum and with or without regional data. Use of the village median arsenic level introduced misclassification bias, by including villages with levels >500 µg/L, but use of the village mean or the maximum did not, and showed significant negative cancer slope factors for models of bladder cancers and of bladder and lung cancers combined. Inclusion of the southwest Taiwan regional data (external reference region) did not change the findings when the model contained an explanatory variable for non-arsenic differences. A positive slope could only be generated by including the comparison population as a separate data point with the assumption of zero arsenic exposure from drinking water and eliminating the variable for non-arsenic risk factors.
Lin et al. 2013. Arsenic levels in drinking water and mortality of liver cancer in Taiwan. Evaluated the dose-response between arsenic in drinking water and mortality of liver cancer in 138 villages in the southwest Taiwan. Assessed arsenic levels in drinking water using data from a survey conducted by the government and reviewed death certificates from 1971 to 1990 to identify liver cancer cases. Using village as the unit, conducted multivariate regression analyses and then performed post hoc analyses to validate the findings. During the 20-year period, 802 male and 301 female mortality cases of liver cancer were identified. After adjusting for age, arsenic levels above 0.64 mg/L were associated with an increase in the liver cancer mortality in both genders, but no significant effect was observed for lower exposure categories.
Liu-Mares et al. 2013. Pancreatic cancer clusters and arsenic-contaminated drinking water wells in Florida. Examined if clusters of persons diagnosed with pancreatic cancer were more likely to be located near arsenic-contaminated drinking water wells, 5,707 arsenic samples were collected from December 2000 to May 2008 from > 5,000 privately owned wells. Spatial modeling was applied to pancreatic cancer cases diagnosed 1998-2002 in Florida (n = 11,405). Multivariable logistic regression was used to determine if sociodemographic indicators, smoking history, and proximity to arsenic-contaminated well sites were associated with residence at the time of pancreatic cancer diagnosis occurring within versus outside a cluster. Spatial modeling identified 16 clusters in which 22.6% of all pancreatic cancer cases were located. Cases living within 1 mile of known arsenic-contaminated wells were significantly more likely to be diagnosed within a cluster of pancreatic cancers relative to cases living more than 3 miles from known sites (OR = 2.1 [95% CI = 1.9, 2.4]).
Luo et al. 2011. Association between six environmental chemicals and lung cancer incidence in the United States. Used the Toxics Release Inventory (TRI) database and Surveillance, Epidemiology, and End Results (SEER) data to conduct an ecological study at the county level. Used multiple linear regression to assess the association of age-adjusted lung cancer incidence with the quantities of on-site air and water releases of six selected industrial chemicals including arsenic, 1,3 butadiene, cadmium, chromium, formaldehyde, and nickel after controlling for other risk variables. Found a significantly increased risk of lung cancer incidence associated with releases of chromium, formaldehyde, and nickel, for both males and females, only in nonmetropolitan counties. Releases of arsenic, 1,3 butadiene, and cadmium were reported by small numbers of facilities, and no relationships to lung cancer incidence were detected.

Figure 9.30u. ORNL Review: Chapter 7 List of Ecological Studies, Part 2

TABLE 3. Arsenic and Cancer Endpoints – Ecological Studies 2009-2013
Martinho and Freitas. 2009. Spatial regression analysis between air pollution and childhood leukaemia in Portugal. Investigated if carcinogenic chemical elements in atmospheric deposition are associated with child mortality due to leukemia in a Portuguese population. A Bayesian hierarchical model was used to explore the association between lichen biomonitoring measurements of four elements: As, Hg, Ni, Pb, and childhood leukemia death counts taken at small administrative units. This geographical epidemiological study found a non-significant positive association between the risk of childhood leukemia and levels of arsenic, mercury and lead, and a non-significant negative association between the disease and the level of nickel.
Navoni et al. 2012. [Health risk for the vulnerable population exposed to arsenic in the province of Buenos Aires, Argentina]. (Spanish). Analyzed water arsenic concentration in Buenos Aires, Argentina, and its relationship susceptibility and associated pathologies in 152 samples at 52 localities from 2003-2008. A composite index of health (CIH) was constructed using the content of arsenic and the percentages of households with unmet basic needs and dwellings without access to the potable water. Concentrations of arsenic spanned a broad range from 0.3 to 187 mg/L, with a median of 40 mg/L. Of the samples, 82% presented levels of arsenic higher than the acceptable limit of 10 mg/L, and more than half of those came from households with potable water connections. In the departments studied, the average mortality (deaths/100 000 inhabitants) from tumors was greater in men than in women: respiratory tract (310 versus 76), urinary tract (44 versus 11), and skin (21 versus 11), respectively. The regions with greater concentrations of arsenic and of poverty, together with the lack of potable water, had a two-to-four times greater risk.
Nieder et al. 2009. Bladder cancer clusters in Florida: identifying populations at risk. Identified high risk bladder cancer areas and risk factors associated with bladder cancer clusters in Florida using individual and area based data. Spatial modeling was applied to 23,266 early and advanced bladder cancer cases diagnosed between 1998 and 2002: A total of 25 clusters had a higher than expected bladder cancer rate, including 13 and 12 of early and late stage disease, respectively. Urban white patients were more likely to live in an advanced bladder cancer cluster. Advanced bladder cancer cluster membership was associated with living in close proximity to known arsenic contaminated drinking water wells.
Pearce et al. 2012. Cancer incidence and soil arsenic exposure in a historical gold mining area in Victoria, Australia: a geospatial analysis. Cancer Registry and geochemical data in the goldfields region of Victoria, Australia were accessed for an ecological geographical correlation study, 1984-2003. Spatial empirical Bayes smoothing was applied when estimating standardized incidence ratios (SIRs) for cancers in 61 statistical local areas. The soil arsenic exposure ranged from 1.4 to 1857 mg/kg. Spatial autoregressive modelling detected increases in smoothed SIRs for all cancers of 0.05 (95% CI, 0.02-0.08) and 0.04 (0.01-0.07) per 2.7-fold increase in the natural log-transformed exposure metric for males and females, respectively, in more socioeconomically disadvantaged areas; for melanoma in males (0.05 (0.01-0.08) adjusted for disadvantage) and females (0.05 (0.02-0.09) in disadvantaged areas). Excess risks were estimated for all cancers (relative risk 1.21 (95% CI, 1.15-1.27) and 1.08 (1.03-1.14)), and melanoma (1.52 (1.25-1.85) and 1.29 (1.08-1.55)), for males and females, respectively, in disadvantaged areas in the highest quintile of the exposure metric relative to the lowest.

Figure 9.30v. ORNL Review: Chapter 7 List of Ecological Studies, Part 3

TABLE 3. Arsenic and Cancer Endpoints – Ecological Studies 2009-2013
Pou et al. 2011. Bladder cancer mortality trends and patterns in Córdoba, Argentina (1986-2006). A joinpoint regression was performed to compute the estimated annual percentage changes (EAPC) of the age-standardized mortality rates (ASMR) in an adult population from Córdoba, Argentina. A Poisson model was fitted to estimate the effect of age, period, and cohort. The influence of gender, tobacco smoking (using lung cancer ASMR as surrogate), and arsenic in drinking water was examined using a hierarchical model. A decreasing trend (1986-2006) in bladder cancer ASMR in both sexes was found: EAPC of -2.54 in men and -1.69 in women. Statistically significant increases in mortality due to bladder cancer, compared to female low exposure group, were seen in females and males exposed to 320–1800 µg/L iAs (RR=4.71 for males, 1.22 for females), and in males exposed to 40-320 µg/L (RR=4.03), and 0–40 µg/L (RR=3.14) iAs. A non-random space-time distribution of the rates was observed. There has been a decreasing trend in ASMR for bladder cancer in Córdoba. Bladder cancer was associated with age, gender, smoking habit, and exposure to arsenic. **Cohen et al. 2013 Comment:** The results of this study highly are uncertain because (1) bladder cancer rates for highly exposed men were compared with rates for low exposed women, in spite of differences between Argentinean men and women in bladder cancer rates; (2) lung cancer mortality rates were used as a surrogate variable to adjust for smoking status; and (3) the reduction in overall bladder cancer mortality rates over time was attributed to reduced exposure to arsenic due to improvements in water quality, but did not address other potential causes such as improved medical care, early detection, decreased smoking incidence, and various lifestyle improvements.
Putila and Guo. 2011. Association of arsenic exposure with lung cancer incidence rates in the United States. Measurements of arsenic stream sediment and soil concentration obtained from the USGS National Geochemical Survey were combined, respectively, with 2008 BRFSS estimates on smoking prevalence and 2000 U.S. Census county level income to determine the effects of these factors on lung cancer incidence, as estimated from respective state-wide cancer registries and the SEER database. Poisson regression was used to determine the association between each variable and age-adjusted county-level lung cancer incidence. ANOVA was used to assess interaction effects between covariates. Sediment levels of arsenic were significantly associated with an increase in incident cases of lung cancer ($P<0.0001$). These effects persisted after controlling for smoking and income ($P<0.0001$). There was also a significant interaction between arsenic exposure levels and smoking prevalence ($P<0.05$).
Smith et al. 2012. Mortality in young adults following in utero and childhood exposure to arsenic in drinking water. The city of Antofagasta in northern Chile was exposed to high arsenic concentrations (870 µg/L) from 1958 to 1970 when an arsenic-removal plant commenced operations. Compared mortality data between Antofagasta and the rest of Chile for people 30-49 years of age during 1989-2000. Estimated expected deaths from mortality rates in all of Chile, excluding Region II where Antofagasta is located, and calculated standardized mortality ratios (SMRs). Found evidence of increased mortality from bladder cancer [SMR = 18.1; 95% confidence interval (CI): 11.3, 27.4], laryngeal cancer (SMR = 8.1; 95% CI: 3.5, 16.0), liver cancer (SMR = 2.5; 95% CI: 1.6, 3.7), and chronic renal disease (SMR = 2.0; 95% CI: 1.5, 2.8). Thus, arsenic in Antofagasta drinking water resulted in the greatest increases in mortality in adults < 50 years of age ever associated with early-life exposure.
Su et al. 2010. Incidence of oral cancer in relation to nickel and arsenic concentrations in farm soils of patients' residential areas in Taiwan. This study utilized the age-standardized incidence rates of oral cancer in the 316 townships and precincts of Taiwan, local prevalence rates of cigarette smoking and betel quid chewing, demographic factors, socio-economic conditions, and concentrations in farm soils of 8 heavy metals. Spatial regression and GIS were used. The registration contained 22,083 patients, who were diagnosed with oral cancer between 1982 and 2002. The concentrations of metal in the soils were retrieved from a nation-wide survey in the 1980s. The incidence rate of oral cancer was geographically related to the concentrations of arsenic and nickel in the patients' residential areas, with the prevalence of cigarette smoking and betel quid chewing as controlled variables.

Figure 9.30w. ORNL Review: Chapter 7 List of Ecological Studies, Part 4

TABLE 3. Arsenic and Cancer Endpoints – Ecological Studies 2009-2013
Yorifuji et al. 2011. Cancer excess after arsenic exposure from contaminated milk powder. Examined whether birth cohorts in western Japan (Okayama Prefecture) that drank arsenic-contaminated milk powder during early summer in 1955 experienced increased cancer mortality. Targeted subjects who were born from September 1950 to August 1960 and died in Okayama Prefecture between January 1969 and March 2008 due to malignant neoplasm (N = 3,141). Compared cancer mortality (total, liver, pancreatic, lung, bladder/kidney, and hematopoietic cancers) between cohorts born before and after the milk poisoning (exposed/nonexposed groups). Total and liver cancers were elevated in the cohort up to 1 year of age at time of poisoning. Pancreatic and hematopoietic cancers were elevated in cohorts up to 5 years of age, and mortality ratios were 2x those of the non-exposed group. Increased risk of lung and bladder/kidney cancers was not apparent. Thus, developmental arsenic exposure may lead to a different pattern of cancer compared with adult or lifetime exposures to inorganic arsenic.
OR = Odds ratio

Figure 9.30x. ORNL Review: Chapter 7 List of Ecological Studies, Part 5

VIII. DERMAL STUDIES:

A number of epidemiological studies evaluated the relationship between exposure to arsenic and development of skin lesions. These studies are significant because it has been proposed that skin lesions occur at a lower exposure, and are a precedent to, cancer of the skin and internal organs such as the lung and bladder. Arsenic exposure was based on intake of arsenic-contaminated water in all but two studies.

Several prospective cohort studies, which are generally considered best suitable for determining a causal dose-response relationship, were published between 2009 and 2013, and considered relevant to an arsenic-cancer dose-response assessment. Hsu et al. (2013b) found that hyperkeratosis was associated with an increased lung cancer risk in an arseniasis-endemic area in Taiwan, and that subjects with skin cancers had an increased risk of lung cancer and urothelial carcinoma compared to those without skin lesions (hyperpigmentation, hyperkeratosis, or Bowen's disease). Argos et al. (2011) found that chronic arsenic exposure from drinking water was associated with increased incidence of skin lesions, even at arsenic levels below 100 µg/L, using data from a cohort of over 10,000 Bangladeshi adults. Evaluation of the same cohort showed that low intake of various nutrients, a diet low in "gourds and roots," smoking, fertilizer use, and selected variants of the arsenic methyltransferase gene (AS3MT) strengthened the association between water arsenic and skin lesion incidence (Melkonian et al. 2011; 2012; Pierce et al. 2011; 2012).

The majority of studies that examined the association of arsenic exposure and skin lesions or cancer were case-control studies, many of which considered the impact of subject variability on the association. Dennis et al. (2010) found a suggested association between ever use of arsenical pesticides and skin cancers in pesticide applicators in North Carolina, U.S. The risk of skin squamous cell carcinoma in a New Hampshire, U.S. population was correlated with levels of urinary total arsenic and arsenic metabolites MMA and DMA (Gilbert-Diamond et al. 2013). Dastgiri et al. (2010) found an association between arsenic levels in the drinking water and dermal lesions (hyperkeratosis and skin pigmentation), hypertension, and chromosomal abnormalities in a rural Iranian community. Bencko et al. (2009) found a positive correlation between the incidence of non-melanoma skin cancer and exposure to arsenic from burning arsenic-rich coal in Slovakia, based on arsenic levels in hair. A multi-country study (Hungary, Romania, and Slovakia) found a correlation between the incidence of basal cell carcinoma and lifetime intake of inorganic arsenic (Leonardi et al., 2012), as well as an increased risk of nonmelanoma skin cancer from workplace inhalation exposure to arsenic in dust and fumes (Surdu et al., 2013). Bangladeshi men who smoked cigarettes and women who chewed tobacco had an increased risk of arsenic-related skin lesions, as did adults with hypomethylated leukocyte DNA at recruitment, compared to respective referent groups (Lindberg et al. 2010; Pilsner et al., 2009).

The risk for developing arsenic-related skin lesions in an Indian population was increased by polymorphisms in the promoters of the TNF-α and IL10 genes; polymorphisms of the coding region of the genes for NALP2 (inflammasome), XRCC3 T241 (recombination repair), and AS3MT; and hypermethylation of the promoters of the p16 (tumor suppressor) and death-associated protein kinase genes (Banerjee et al. 2011; 2013; Kundu et al., 2011; Bhattacharjee et

Figure 9.30y. ORNL Review: Chapter 8 Dermal Studies

al., 2013). Several polymorphisms of the metabolic ASTM3 gene increased the risk of arsenic-related skin lesions in a Mexican population.

In a cross-sectional study, Paul et al. (2013) found a significantly lower incidence and severity of dermatological disorders at a lower exposure to arsenic in the drinking water in West Bengal, India. In an ecological study conducted in 326 areas in England, no association was found between environmental arsenic and the rates of non-melanoma skin cancer (Wheeler et al. 2013).

Summaries of the published abstracts for these dermal-related studies, as well as the first author and title, are presented in Table 4. Studies are listed alphabetically by first author.

Figure 9.30z. ORNL Review: Chapter 8 Dermal Studies, cont.

TABLE 4. Arsenic and Cancer Endpoints – Dermal Studies 2009-2013

Author, Title; Abstract Summary (listed alphabetically)

Argos et al. 2011. A prospective study of arsenic exposure from drinking water and incidence of skin lesions in Bangladesh.
Used participants in the Health Effects of Arsenic Longitudinal Study (HEALS). The analyses used data on 10,182 adults free of skin lesions at baseline through the third biennial follow-up of the cohort (2000–2009). Discrete-time hazard regression models were used to estimate hazard ratios and 95% confidence intervals for incident skin lesions. Multivariate-adjusted hazard ratios for incident skin lesions comparing 10.1–50.0, 50.1–100.0, 100.1–200.0, and ≥200.1 μg/L with ≤10.0 μg/L of well water arsenic exposure were 1.17 (95% CI: 0.92, 1.49), 1.69 (95% CI: 1.33, 2.14), 1.97 (95% CI: 1.58, 2.46), and 2.98 (95% CI: 2.40, 3.71), respectively (P_{trend} = 0.0001). Results were similar for the other measures of arsenic exposure, and the increased risks remained unchanged with changes in exposure in recent years. Dose-dependent associations were more pronounced in females, but the incidence of skin lesions was greater in males and older individuals. Chronic arsenic exposure from drinking water was associated with increased incidence of skin lesions, even at low arsenic exposure levels (<100 μg/L).

Banerjee et al. 2011. Polymorphisms in the TNF-α and IL10 gene promoters and risk of arsenic-induced skin lesions and other nondermatological health effects.
A case-control study in West Bengal, India, involved 207 cases with arsenic-induced skin lesions and 190 controls without skin lesions having similar arsenic exposure. The polymorphisms were determined using conventional PCR-sequencing method. ELISA was done to determine serum levels of TNF- α and interleukin 10 (IL10). Associations between the polymorphisms and nondermatological health effects in subjects were determined from survey data. Individuals with GA/AA (2308 TNF-a) and TA/AA (23575 IL10) genotypes were at higher risk of developing arsenic-induced skin lesions, ocular, and respiratory diseases. The 2308 TNF A allele corresponded to a higher production of TNF- α, and 23575 IL10 A allele corresponded to a lower production of IL10. Thus both TNF-α (–308G>A) and IL10 (–3575 T>A) SNPs render individuals susceptible toward developing arsenic-induced skin lesions, which have the potential to develop into cancerous skin lesions.

Banerjee et al. 2013. Epigenetic modifications of DAPK and p16 genes contribute to arsenic-induced skin lesions and nondermatological health effects.
To elucidate the role of promoter methylation in arsenic-induced dermatological and nondermatological health effects, methylation status of tumor suppressor genes p16 and death-associated protein kinase (DAPK) was determined by bisulfite conversion of genomic DNA and methylation-specific PCR. A case-control study was conducted involving 72 individuals with arsenic-induced skin lesions (cases) and 50 individuals without skin lesions (controls), having similar arsenic exposure through drinking water. Expression of the genes was determined by real-time PCR and Western blot analysis. Associations between the promoter methylation status and health effects were determined from survey data. Significant hypermethylation was found in the promoters of both DAPK and p16 genes in the cases resulting in down-regulation of both the genes. There was a 3.4-fold decrease in the expression of DAPK and 2.2-fold decrease in gene expression of p16 in the cases compared to the controls, the lowest expression being in the cancer tissues. Promoter hypermethylation of the genes was also associated with higher risk of developing arsenic-induced skin lesions, peripheral neuropathy, ocular and respiratory diseases.

Bencko et al. 2009. Ecological and human health risk aspects of burning arsenic-rich coal.
Arsenic-rich coal is burned in Central Slovakia to fuel power plants. The criterion of higher exposure for persons living near a power plant was arsenic content in hair exceeding concentrations of 3 μg/g hair in 10-year old boys. The referent group was people who lived >7.5 miles from the power plant. Evaluated database of 1,503 non-melanoma skin cancer (NMSC) cases (756 in men and 747 in women) collected from 1977 to 1996 (population ~ 125,000). The age standardized incidence of NMSC (each confirmed by histological examination) in non-occupational settings ranged from 45.9 to 93.9 in men and from 34.6 to 81.4 in women. The data demonstrate a positive correlation between human cumulative exposure to arsenic and incidence of NMSC.

Figure 9.30aa. ORNL Review: Chapter 8 List of Dermal Studies, Part 1

TABLE 4. Arsenic and Cancer Endpoints – Dermal Studies 2009-2013
Bhattacharjee et al. 2013. Association of NALP2 polymorphism with arsenic induced skin lesions and other health effects. Investigated association between arsenicism and the exonic single nucleotide polymorphisms (SNPs) in the NALP2 gene, an important component of inflammasome complex, in 432 arsenic-exposed individuals, 219 with arsenic-induced skin lesions (cases) and 213 without (controls), from West Bengal, India. Among 9 SNPs, the A1052E polymorphism (at least with one minor allele), was overrepresented in controls and implies decreased risk for skin lesions [OR=0.67, 95% CI: 0.46-0.97]. Also attempted to correlate the genetic variation of NALP2 with chromosomal aberration, peripheral neuropathy, eye problems, and respiratory diseases. Individuals with the protective genotype had less chromosomal aberration ($p<0.05$), and were also less susceptible toward arsenic-related respiratory diseases [OR=0.47; 95%CI: 0.23-0.89].
Dastgiri et al. 2010. Arsenic exposure, dermatological lesions, hypertension, and chromosomal abnormalities among people in a rural community of northwest Iran. The occurrence of dermatological lesions, hypertension, and chromosomal abnormalities was investigated in 101 subjects with chronic exposure to arsenic in drinking-water and 107 subjects with no exposure. Daily/yearly absorbed amounts of arsenic and the cumulative arsenic index were calculated for all subjects. Arsenic concentration in drinking-water sources was 1031 +/- 1103 µg/L and non-detectable, respectively. The mean systolic blood pressure and diastolic blood pressure were significantly higher than that in the control group. The incidence of hyperkeratosis was 34 times higher among the exposure group compared to the control subjects [OR=34, $p<0.001$)]. A significant difference was also observed in the occurrence of skin-pigmentation between the two groups (OR=2.4, $p<0.007$). Location and severity of the pigmentations were statistically different between the two groups. Twenty-five percent of the subjects in the exposure group showed chromosomal abnormalities ($p=0.05$).
Dennis et al. 2010. Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. Farmers have shown an excess risk of melanoma and other skin cancers. To determine how much of this is related to sun exposure compared with other agricultural exposures, examined dose-response relationships for 50 agricultural pesticides and cutaneous melanoma. Logistic regression showed significant associations between cutaneous melanoma and maneb/mancozeb (≥ 63 exposure days: OR = 2.4; 95% CI, 1.2-4.9; trend p = 0.006), parathion (≥ 56 exposure days: OR = 2.4; 95% CI, 1.3-4.4; trend p = 0.003), and carbaryl (≥ 56 exposure days: OR = 1.7; 95% CI, 1.1-2.5; trend p = 0.013). Other associations with benomyl and ever use of arsenical pesticides were also suggested.
Gilbert-Diamond et al. 2013. A Population-based Case-Control Study of Urinary Arsenic Species and Squamous Cell Carcinoma in New Hampshire, USA. Estimated associations between total urinary arsenic and arsenic species and squamous cell carcinoma (SCC) in a U.S. population by a case-control study (470 cases, 447 controls) in a region with moderate arsenic exposure through private well water and diet. Measured urinary iAs, MMA, and DMA, and summed these arsenic species (ΣAs). Participants who reported seafood consumption within 2 days before urine collection were excluded from the analyses. In adjusted logistic regression analyses (323 cases, 319 controls), the SCC odds ratio (OR) was 1.37 for each ln-transformed µg/L increase in ln-transformed ΣAs concentration [ln(ΣAs)] (95% CI: 1.04, 1.80). Urinary ln(MMA) and ln(DMA) also were positively associated with SCC (OR = 1.34; 95% CI: 1.04, 1.71 and OR = 1.34; 95% CI: 1.03, 1.74, respectively). A similar trend was observed for ln(iAs) (OR = 1.20; 95% CI: 0.97, 1.49). Percent iAs, MMA, and DMA were not associated with SCC. Thus, arsenic exposure at levels common in the U.S. is related to SCC, and arsenic metabolism ability does not modify the association.

Figure 9.30bb. ORNL Review: Chapter 8 List of Dermal Studies, Part 2

TABLE 4. Arsenic and Cancer Endpoints – Dermal Studies 2009-2013
Hsu et al. 2013b. Use of arsenic-induced palmoplantar hyperkeratosis and skin cancers to predict risk of subsequent internal malignancy. A prospective (17-year follow-up) study examined the association between arsenic-induced skin lesions (hyperpigmentation, hyperkeratosis, and Bowen's disease) and subsequent internal cancers in an arseniasis-endemic area in southwestern Taiwan, where 2,447 residents participated in skin examinations during the late 1980s. The number of participants diagnosed with hyperpigmentation was 673; with hyperkeratosis, 243; and with skin cancer (Bowen's disease or non-melanoma skin cancer), 378. Cox regression showed that patients affected with skin cancers had an increased risk of lung cancer (hazard ratio = 4.64, 95% CI: 2.92, 7.38) and urothelial carcinoma (hazard ratio = 2.02, 95% confidence interval: 1.23, 3.30) compared to participants without skin lesions, after adjustment for potential confounders and cumulative arsenic exposure. Hyperkeratosis is significantly associated with an increased lung cancer risk (hazard ratio = 2.76, 95% CI: 1.35, 5.67). A significant interactive effect on lung cancer risk between hyperkeratosis and cigarette smoking was also identified. **Commentary: Ahsan and Steinmaus. 2013. Use of arsenical skin lesions to predict risk of internal cancer: implications for prevention and future research.** Consider the study by Hsu et al. (2013b) to be methodologically limited, in that the cumulative arsenic exposure may not reflect an individual's actual exposure, and that skin lesions classified as "low exposure" were likely to be incorrectly classified. Despite the methodological limitations, felt that the findings underscore the need for assessing whether dermatological manifestations are also predictive of non-cancer, long-term health consequences. **Author Reply: Hsu and Chen. 2013. Hsu and Chen respond to "implications for prevention and future research".** Authors considered misclassification of arsenic exposure to be nondifferential between subjects with or without arsenic skin lesions. And the extent of biased estimation of the relative risk was small. **Commentary: Alberg AJ. 2013. "Use of arsenic-induced palmoplantar hyperkeratosis and skin cancers to predict risk of subsequent internal malignancy."** Results of Hsu et al. (2013b) are consistent with an accruing body of evidence that non-melanoma skin cancer (NMSC) is a marker of a cancer-prone phenotype and elevated risk of other malignancies. The association has been observed for both squamous cell and basal cell carcinoma, in men and women. Notable study aspects include its design (whole population was assessed by dermatologists), and its Asian ethnicity.
Kundu et al. 2011. Precancerous and non-cancer disease endpoints of chronic arsenic exposure: the level of chromosomal damage and XRCC3 T241M polymorphism. A case-control study was conducted in West Bengal, India, involving 206 cases with arsenic-induced skin lesions and 215 controls without arsenic-induced skin lesions having similar arsenic exposure. Polymorphism at the XRCC3 T241M gene (a homologous recombination repair pathway gene) was determined using conventional PCR-sequencing. Chromosomal aberration assay, arsenic-induced neuropathy and ocular diseases were also evaluated. The data revealed that presence of at least one Met allele (Met/Met or Thr/Met) was protective towards development of arsenic-induced skin lesions [OR=0.45, 95% CI: 0.30-0.67], peripheral neuropathy [OR=0.49; 95%CI: 0.30-0.82] and conjunctivitis [OR=0.60; 95%CI: 0.40-0.92]. A significant correlation was also observed between protective genotype and decreased frequency of chromosomal aberrations.

Figure 9.30cc. ORNL Review: Chapter 8 List of Dermal Studies, Part 3

TABLE 4. Arsenic and Cancer Endpoints – Dermal Studies 2009-2013
Leonardi et al. 2012. Inorganic arsenic and basal cell carcinoma in areas of Hungary, Romania, and Slovakia: a case-control study. The Arsenic Health Risk Assessment and Molecular Epidemiology (ASHRAM) study, a case-control study, was conducted in areas of Hungary, Romania, and Slovakia with reported presence of iAs in groundwater. Cases of basal cell carcinoma (BCC) were confirmed histologically; controls were hospital patients matched to cases by age, sex, and area of residence. Exposure indices were based on iAs intake over the lifetime of participants. iAs metabolism status was classified based on urinary concentrations of MMA and DMA. Associations were estimated by multivariable logistic regression for the 529 cases with BCC and 540 controls. BCC was positively associated with peak daily iAs dose rate, cumulative iAs dose, and lifetime average water iAs concentration. The adjusted OR per 10-µg/L increase in average lifetime water iAs concentration was 1.18 (95% CI: 1.08, 1.28). The estimated effect of iAs on cancer was stronger in participants with urinary markers indicating incomplete metabolism of iAs: higher percentage of MMA in urine or a lower percentage of DMA. Found a positive association between BCC and exposure to iAs through drinking water with concentrations <100 µg/L.
Lindberg et al. 2010. Impact of smoking and chewing tobacco on arsenic-induced skin lesions. To elucidate interactions between tobacco use and arsenic metabolism on the risk of developing skin lesions, used a case-referent study that showed increased risk for skin lesions in relation to chronic arsenic exposure via drinking water in Bangladesh. Randomly selected 526 of the referents (> 4 years old; 47% male) and all 504 cases (54% male) with arsenic-related skin lesions to measure arsenic metabolites MMA and DMA in urine. The OR for skin lesions was almost 3x higher in the highest tertile of urinary %MA than in the lowest tertile. Men who smoked cigarettes and bidis had a significantly higher risk for skin lesions than did nonsmoking men. Women who chewed tobacco had a higher risk of skin lesions than did women who did not use tobacco.
Melkonian et al. 2012. Intakes of several nutrients are associated with incidence of arsenic-related keratotic skin lesions in Bangladesh. Prospectively evaluated the association of nutrient intake and gender with incident arsenic-related skin lesions using data from the Health Effects of Arsenic Longitudinal Study (HEALS) in Araihazar, Bangladesh. Discrete time hazard models were used to estimate these effects in stratified analyses based on skin lesion severity. Overall, observed significant associations between low intakes of various nutrients (retinol, calcium, fiber, folate, iron, riboflavin, thiamin, and vitamins A, C, and E) and skin lesion incidence, particularly for keratotic skin lesions. Associations for vitamins C and E showed significant linear trends. Gender-specific analyses revealed an inverse association between the lowest quartile of nutrient intake and keratotic skin lesion incidence for retinol equivalents, calcium, folate, iron, and fiber among women. Interactions by gender were observed for retinol equivalents, calcium, vitamin A, and riboflavin with the incidence of keratotic skin lesions.
Melkonian et al. 2011. A prospective study of the synergistic effects of arsenic exposure and smoking, sun exposure, fertilizer use, and pesticide use on risk of premalignant skin lesions in Bangladeshi men. Prospectively evaluated synergisms between effects of arsenic exposure and those of tobacco use, sun exposure, and pesticide and fertilizer use on incident skin lesions using risk factor data from 5,042 men from the Health Effects of Arsenic Longitudinal Study (HEALS) in Araihazar, Bangladesh, which recruited participants from October 2000 to May 2002. Discrete time hazard models were used to estimate measures of synergistic interactions on the additive scale. Found significant synergistic effects between various measures of arsenic exposure and smoking and fertilizer use. The relative excess risks for the interactions between smoking status and arsenic exposure were 0.12 (95% CI: 0.06, 0.19) for water arsenic and 0.11 (95% CI: 0.05, 0.15) for urinary arsenic measures, respectively. Significant synergistic effects were also observed between fertilizer use and water arsenic (relative excess risk for the interaction = 0.06, 95% CI: 0.01, 0.12).

Figure 9.30dd. ORNL Review: Chapter 8 List of Dermal Studies, Part 4

TABLE 4. Arsenic and Cancer Endpoints – Dermal Studies 2009-2013
Paul et al. 2013. Arsenic-induced toxicity and carcinogenicity: a two-wave cross-sectional study in arsenicosis individuals in West Bengal, India. A cross-sectional study was conducted in West Bengal, India, where 189 arsenicosis and 171 unexposed individuals were recruited at two time points, (2005-06 and 2010-11) with concomitant decrease in the level of arsenic exposure via drinking water in the arsenicosis group in 2010-11. Parameters studied included dermatological, non-dermatological health status and cytogenetic damage. Decrease of arsenic exposure (190.1 µg/l to 37.94 µg/l) resulted in significant decline in the number of individuals having dermatological disorders ($P<0.01$) and in the severity of each dermatological outcome ($P<0.0001$). Micronucleus formation in urothelial cells and lymphocytes decreased significantly ($P<0.001$). However, there was a significant ($P<0.001$) rise in the incidence of peripheral neuropathy, conjunctivitis, and respiratory distress. Thirteen (6.87%) of the initially recruited arsenicosis individuals died of cancer in this period.
Pierce et al. 2011. Arsenic exposure, dietary patterns, and skin lesion risk in Bangladesh: a prospective study. Evaluated associations among dietary patterns, arsenic exposure, and skin lesion risk using baseline food frequency questionnaire data collected in the Health Effects of Arsenic Longitudinal Study (HEALS) in Araihazar, Bangladesh (2000-2009). The authors identified 3 clear dietary patterns: the "gourd and root," "vegetable," and "animal protein" patterns, and tested them for association with incident skin lesion risk and interaction with water arsenic exposure by using ~6 years of follow-up data (814 events among 9,677 individuals) and discrete time hazards models (adjusting for key covariates). The gourd and root pattern score was inversely associated with skin lesion risk (P(trend) = 0.001), with hazard ratios of 0.86, 0.73, and 0.69 for the second, third, and fourth highest quartiles. Furthermore, the association between water arsenic and skin lesion incidence was stronger among participants with low gourd and root scores (multiplicative $P_{interaction} < 0.001$; additive $P_{interaction} = 0.05$). The vegetable pattern and animal protein pattern showed similar but weaker associations and interactions.
Pierce et al. 2012. Genome-wide association study identifies chromosome 10q24.32 variants associated with arsenic metabolism and toxicity phenotypes in Bangladesh. A genome-wide association study (GWAS) of arsenic-related metabolism and toxicity phenotypes used data on urinary arsenic metabolite concentrations and ~ 300,000 genome-wide single nucleotide polymorphisms (SNPs) for 1,313 arsenic-exposed Bangladeshi individuals. Identified genome-wide significant association signals ($P<5\times10^{-8}$) for percentages of both MMA and DMA near the AS3MT gene (arsenite methyltransferase; 10q24.32), with five genetic variants showing independent associations. In a follow-up analysis of 1,085 individuals with arsenic-induced premalignant skin lesions and 1,794 controls, one of these five variants (rs9527) was also associated with skin lesion risk ($P=0.0005$). In a subset of individuals with prospectively measured arsenic (n=769), rs9527 interacted with arsenic to influence incident skin lesion risk ($P=0.01$). Expression quantitative trait locus (eQTL) analyses of genome-wide expression data from 950 individuals' lymphocyte RNA suggest that several SNPs represented cis-eQTLs for AS3MT ($P=10^{-12}$) and neighboring gene C10orf32 ($P=10^{-44}$).
Pilsner et al. 2009. Folate deficiency, hyperhomocysteinemia, low urinary creatinine, and hypomethylation of leukocyte DNA are risk factors for arsenic-induced skin lesions. Evaluated whether As-induced skin lesion risk in Bangladeshi adults is associated with poor methylation capacity in a nested case-control study of 274 cases who developed lesions 2 years after recruitment, and 274 controls matched to cases for sex, age, and water As. The OR and 95% CIs for development of skin lesions for participants who had low folate (< 9 nmol/L), hyperhomocysteinemia (men, > 11.4 µmol/L; women, > 10.4 µmol/L), or hypomethylated leukocyte DNA at recruitment (< median) were 1.8 (95% CI, 1.1-2.9), 1.7 (95% CI, 1.1-2.6), and 1.8 (95% CI, 1.2-2.8), respectively. Compared with the subjects in the first quartile, those in the third and fourth quartiles for urinary creatinine had a 0.4-fold decrease in the odds of skin lesions ($p < 0.01$).

Figure 9.30ee. ORNL Review: Chapter 8 List of Dermal Studies, Part 5

TABLE 4. Arsenic and Cancer Endpoints – Dermal Studies 2009-2013
Surdu et al. 2013. Occupational exposure to arsenic and risk of nonmelanoma skin cancer in a multinational European study. This case-control study assessed airborne arsenic exposures at the workplace and quantified associations with nonmelanoma skin cancer (NMSC) in 618 incident cases of NMSC and 527 hospital-based controls aged 30-79 years from Hungary, Romania and Slovakia. Exposures were evaluated using occupational histories. Information on host factors and other exposures was collected and used to adjust the associations of interest using multivariable logistic regression. The lifetime prevalence of exposure to work-related arsenic is 23.9% for cases and 15.5% for controls. No significant association between arsenic exposure in the workplace and NMSC was detected, although an increased adjusted OR was observed for participants with higher cumulative lifetime workplace exposure to arsenic in dust and fumes compared to referents [OR = 1.94, 95% CI = 0.76-4.95]. This association was modified in women in the presence of workplace sunlight exposure with a markedly increased adjusted OR (OR = 10.22, 95% CI = 2.48-42.07).
Wheeler et al. 2013. Geography of non-melanoma skin cancer and ecological associations with environmental risk factors in England. Investigated the geography of non-melanoma skin cancer (NMSC) in England, and ecological associations with three widespread environmental hazards: radon, arsenic and uv radiation from the sun. Age-/sex-standardized registration rates of NMSC were mapped for local authority (LA) areas (n=326), along with geographical data on bright sunshine, household radon and arsenic. There was a substantial geographical variation in NMSC rates across English LAs and between cancer registration regions. No association was observed between environmental arsenic and NMSC rates. Rates were associated with area-mean bright sunshine hours, and an association with area-mean radon concentration was suggested.
OR=Odds ratio; MMA =monomethylarsonic acid; DMA=dimethylarsinic acid

Figure 9.30ff. ORNL Review: Chapter 8 List of Dermal Studies, Part 6

IX. SUMMARY AND CONCLUSIONS

Seventy-five studies were selected from the initial online search (PubMed, Toxline, and the Web of Knowledge) as being relevant to Assignment 2, per the WA 2013-05 instructions, which are presented in Section I. These articles provided "Support for the arsenic dose-response model for the quantitative cancer risk assessment." The study inclusion criteria were described in Section III: only studies that evaluated the arsenic-cancer dose-response relationship, which were published from 2009 forward, and that were not discussed in the JECFA Monograph 8 (2011) Arsenic report.

Based on the initial evaluation of these 75 studies, it appears that chronic ingestion of water containing >100 µg/L arsenic is associated with cancer in humans. In a recent analysis of arsenic mechanistic and epidemiological studies, Cohen et al. (2013) asserted that arsenic carcinogenicity has a mode of action that involves cytotoxicity and regenerative proliferation, which "implies a non-linear, threshold dose-response relationship", and that the threshold for carcinogenicity appears to be approximately 100-150 µg/L in the drinking water. Several recent epidemiological studies did, however, suggest that lower water concentrations may cause cancer, and these should be carefully evaluated.

Of the 75 studies that were evaluated, 18 appear to be good candidates for further data analysis, based on the quality of the study methodology, and availability of reliable arsenic exposure data (measurements of arsenic in drinking water, and in one case, in the diet). These studies are as follows:

Cohort studies:
Argos et al. 2011 [dermal]
Chung et al. 2013a
Fernandez et al. 2012
Hsu et al. 2011
Hsu et al. 2013a
Hsu et al. 2013b [dermal]
Liao et al. 2009
Rahman et al. 2013
Sawada et al. 2013
Wade et al., 2009

Case-control studies:
Beebe-Dimmer et al. 2012
Ferreccio et al. 2013
Meliker et al. 2010a
Meliker et al. 2010b
Steinmaus et al. 2013
Wang et al. 2012

Ecological studies:
Lamm et al. 2013
Pou et al. 2011

Figure 9.30gg. ORNL Review: Chapter 9 Summary and Conclusions

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Figure 9.30*oo*. ORNL Review: Chapter 10 References, Part 8

9.6.2 FDA REVIEW OF 18 NEW EPIDEMIOLOGY STUDIES FOUND BY OAK RIDGE LITERATURE REVIEW

The large majority of studies conducted in environmental epidemiology follow study designs that are not intended for dose-response modeling, and as a result, they are not suitable for that purpose. The main shortcomings are as follows:

1) Poor dosimetry. Many studies use biomarkers of exposure that are difficult or impossible to relate to dietary intake. In addition, many of the exposure estimates are based on measures at single time points that may have little bearing on long-term exposure.

2) Case-Control Design. Because they allow the number of cases to be estimated at a given dose, relative risk studies are the most appropriate for dose-response modeling. Unless details are given about the size of the population from which cases are drawn, which is rare, case control studies cannot be used to estimate disease frequency. (However, an odds ratio from a case-control study is a good estimate of relative risk when (1) the "cases" studied are representative of all people with the disease in the population from which the cases were drawn, with regards to history of the exposure; (2) the "controls" studied are representative of all people without the disease in the population from which the cases were drawn, with regards to history of exposure; and (3) the disease being studied is not a frequent one. Under these circumstances, a case-control study could be considered for risk assessment purposes if it otherwise was a well-conducted study.)

3) No clear dose-response trend. Many studies are only designed to establish statistical significance and do not attempt characterize risk as a function of dose.

4) Other significant confounders. Studies where other factors may contribute to the outcome may have their own dose-response relationships that cannot be distinguished from the contribution of arsenic. This is an especially important problem when relative risks are low (i.e. less than 2).

Table 9.16. Evaluation of Epidemiology Studies from Oak Ridge Literature Review

Study	Description	Comments
Argos *et al.*, 2011 (Cohort Study)	HEALS participants. Incidence of skin lesions Bangladesh. 3rd biennial follow up of the cohort.	Not applicable for endpoints considered in FDA model -- lung and bladder cancer

Study	Description	Comments
Chung *et al.*, 2013a (Cohort Study)	Cohort of 1563. Urinary arsenic profiles. Liver (29), lung (71), bladder (43)	This paper only has three levels of dietary exposure, and the middle dose encompasses a very wide range.
Fernandez *et al.*, 2012 (Cohort Study)	Trends of bladder cancer Northern Chile.	No dose-response information, but does characterize temporal trends of male bladder cancer, indicating a peak in 2003, which was 33 years after the episodic exposure to very high levels of arsenic in Antofogasta
Hsu *et al.*, 2011 (Cohort Study)	Measure individual susceptibility. DNA specimens from long term follow up cohort Southernwestern Taiwan. Urothelial carcinoma	Only three doses, not lifetime exposure. Indicates interaction between iAs and smoking for lung cancer, plus minor genetic influence.
Hsu *et al.*, 2013a (Cohort Study)	9525 subjects recruited from cohorts. Associated of diabetes mellitus with internal cancers.	No relative risk for general population. Calculates hazard ratios for individuals with diabetes, which appear to be slightly elevated for many cancers.
Hsu *et al.*, 2013b (Cohort Study)	Prospective (17-yr follow up). Association between arsenic-induced Skin lesions and subsequent internal cancers in an arseniasis-endemic area. Taiwan, 2447 participants. Patients with skin cancer had increased risk of lung cancer and urothelial carcinoma.	Good dose-response data for skin lesions
Liao *et al.*, 2009 (Cohort Study)	8 yr follow up of 10,138 Taiwan. Weibull DR model.	No original data. Modeled same cohorts used by Morales and FDA
Rahman *et al.*, 2013 (Cohort Study)	-	Poor dose-response trend, significant effects only in high dose group.

Study	Description	Comments
Sawada *et al.*, 2013 (Cohort Study)	Prospective study. Arsenic exposure from food (questionnaire data). 90,378. Japan	Low dose exposures, barely significant effect on lung cancer, smokers only
Wade *et al.*, 2009 (Cohort Study)	-	Good dose-response data for all-cause mortality, mortality from all cancers, and heart disease
Beebe-Dimmer *et al.*, 2012 (Case-control Study)	-	Case control, no dose-response
Ferreccio *et al.*, 2013 (Case-control Study)	-	Case control, only three dose groups
Miliker *et al.*, 2010a (Case-control Study)	-	Case control, no dose-response
Miliker *et al.*, 2010b (Case-control Study)	-	Exposure paper
Steinmaus *et al.*, 2013 (Case-control Study)	-	Case-Control. Multiple exposure metrics
Wang *et al.*, 2013 (Case-control Study)	-	Case control, no dose-response
Lamm *et al.*, 2013 (Ecological Study)	-	Same data as Morales
Pou *et al.*, 2011 (Ecological Study)	-	No dose-response.

9.6.3 ARSENIC EXPOSURE BIBLIOGRAPHY

Arsenic Exposure Bibliography_As review Spreadsheet
FINAL_7 Nov 13
ORNL binned and reviewed for Exposure Sample assessment
Prepared by Lee Ann Wilson and Annetta Watson

Key: * (non-US); # (some US); $ (commentary or news article); % (generic ingestion assumptions or no rice-specific data); blank (US)

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9.6.4 ARSENIC IN RICE MARKET SAMPLE BIBLIOGRAPHY

Arsenic Market Sample Bibliography_As review Spreadsheet
FINAL_6 Nov 13
ORNL binned and reviewed for Market Sample assessment
Prepared by Lee Ann Wilson and Annetta Watson

Key: * (non-US); # (some US); $ (commentary or news article); blank (US)

#Adomako E, Solaiman A, Williams P, Deacon C, Rahman G, Meharg A. (2011). Enhanced transfer of arsenic to grain for Bangladesh grown rice compared to US and EU. *Environment International* 35 (3): 476-479.

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Figure 9.32a. ORNL Arsenic Market Sample Bibliography, Part 1

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Figure 9.32b. ORNL Arsenic Market Sample Bibliography, Part 2

9.7 ESTIMATES OF RICE MARKET SHARES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: September 25, 2013

From: Andrew Estrin, Senior Economist, Office of Regulations, Policy and Social Sciences, Center for Food Safety and Applied Nutrition, FDA

Subject: Estimates of Rice Market Shares

To: MEMORANDUM TO FILE

I estimated markets shares for basmati, brown, instant, jasmine, parboiled, long grain, medium grain, and short grain rice types destined for human consumption. Estimates of rice market shares by type are based on data from the 2011/2012 *U.S. Rice Domestic Usage Report* (RDUR) published by the USA Rice Federation (Ref. 1). The data published in the report are from a survey of major rice millers. Twenty-two companies participated in the survey, representing 30 active rice mills. Using the Totals reported in RDUR Table 3 and RDUR Table 8, I estimate that the survey of rice millers accounts for approximately 85 percent of all domestic production destined for domestic markets.

Based on a September 11, 2013 discussion that I had with ERS rice market specialist Nathan Childs, information on quantities of imported rice in the RDUR is from the US Census and reflects 100 percent of imports. This information is available in aggregate (RDUR, Table 5) and also by rice type for the Top-5 importing countries (RDUR Table 6). The total quantities of imports reported in RDUR Table 5 account for 100 percent of imported rice because the data are from the US Census. However, from the RDUR Tables 5 and 6 I estimated that quantities imported from the Top-5 importing countries account for approximately 90 percent of all imported rice.

Figure 9.33a. Memorandum to File: Estimates of Rice Market Shares, Part 1

The distribution of imports across rice types is different than the distribution of domestically produced milled rice across rice types. In order to combine the imported quantities with the domestically produced quantities to meaningfully estimate market shares, I adjusted the quantities of each rice type to reflect 100 percent of imports and domestically produced rice, and then add them together. In order for the estimates to reflect rice for human consumption, I subtracted quantities of rice shipped to pet food manufacturers by type. I then used the resulting totals to estimate the domestic usage market shares for 11 major types of rice as reported in Table 1.

I first modify quantities shipped of each of 9 rice types reported by domestic survey respondents in RDUR Table 11 by adjusting the totals so that they reflect 100 percent of domestically produced rice. I add rows for basmati and jasmine rice types to the table and then add the adjusted quantities of 11 imported rice types reported in RDUR Table 6, and subtract quantities shipped to pet food manufacturers.

According to a September 11, 2013 discussion that I had with ERS rice market specialist Nathan Childs, virtually all jasmine and basmati rice is imported and reported as long grain rice in RDUR Tables 5 and 6 on imports. However, small quantities of basmati and jasmine rice are also reported as specialty types in the RDUR Table 24. The quantities of the rice types reported in RDUR Table 24 would have been obtained from the survey of 22 domestic rice mills, and would also be reported in Table 11 as long grain rice. Consequently, I subtracted quantities of basmati and jasmine rice reported in RDUR Table 24 from the quantity of long grain rice reported in RDUR Table 11, and inserted row categories for basmati and jasmine rice to RDUR Table 11 so that later I could add quantities of imported jasmine and basmati rice reported in RDUR Table 6.

Figure 9.33b. Memorandum to File: Estimates of Rice Market Shares, Part 2

To adjust the quantities reported so that they add to 100 percent rather than 85 percent of production, I inflated shipments of domestically produced rice reported in RDUR Table 11 for long grain, medium grain, brewers/100% broken, short grain, other and rice flour rice types by dividing each of the quantities by 0.85. Shipments of parboiled, brown, jasmine, basmati and instant/pre-cooked types reported in that Table were not inflated since, based on a September 11, 2013 discussion that I had with ERS rice market specialist Nathan Childs, only a small number of mills ship specialty rice types and these would have been counted in the survey. The remaining difference that would have been attributed to those rice types was distributed equally across the already inflated varieties.

I obtained quantities of imported rice by type for the Top-5 importing countries (RDUR, Table 6). Following a September 11, 2013 discussion that I had with ERS rice market specialist Nathan Childs, I learned that virtually all rice imported from Thailand (a top country from which we import rice) is jasmine rice and that virtually all rice imported from India (a top country from which we import rice) is basmati rice. Consequently, I separated long grain imports reported in the RDUR Table 6 into long grain, basmati and jasmine, in order to avoid double counting long grain rice types. In addition, I added the quantity imported of "mixed grain" rice reported in that Table to the long grain totals. To the extent that there are short grain and medium grain rice types included in the "mixed grain" category, I may overstate the amount of long grain rice imported and understate the amounts of short grain and medium grain rice imported.

From RDUR Tables 5 and 6 I estimate that the Top-5 importing countries account for approximately 90 percent of all imported rice, and I multiplied the quantity of each rice type (including basmati, jasmine, and the adjusted long grain quantities) reported in RDUR Table 6 by 1.1, and then added the resulting totals to the adjusted totals for the domestically produced

Figure 9.33c. Memorandum to File: Estimates of Rice Market Shares, Part 3

rice from RDUR Table 11. Since parboiled, brown or instant/pre-cooked rice or other specialty rice types are not included in RDUR Table 6, I may understate the quantities of these types in the combined totals, and overstate the long grain and medium grain types where they would likely be included.

To account only for rice destined for human consumption, I subtracted the total quantities shipped by domestic producers to pet food manufacturers by rice type, reported in RDUR Table 21, from the running total. Although shipments for pet food could also be from imported sources, per a September 11, 2013 discussion that I had with ERS rice market specialist Nathan Childs, only a small number of mills ship to pet food manufacturers and these would have been included in the domestic survey.

Table 1

Rice Type	Shipments (inc. imports) CWT	Shipments adjusted for pet food, CWT	Market Share
Long Grain	31,740,066	31,590,002	37.1%
Medium Grain	15,793,394	15,752,549	18.5%
Brewers/100% Broken	14,523,693	8,866,475	10.4%
Parboiled	7,665,653	7,394,546	8.7%
Brown	2,721,436	2,721,436	3.2%
Jasmine	7,837,477	7,837,477	9.2%
Basmati	2,272,432	2,272,432	2.7%
Other	3,907,788	2,655,927	3.1%
Instant/Pre-cooked	1,986,749	1,986,749	2.3%
Short Grain	2,202,198	2,202,198	2.6%
Rice Flour	1,918,069	1,918,069	2.3%
Total Shipments	92,568,954	85,197,859	100.0%

Figure 9.33d. Memorandum to File: Estimates of Rice Market Shares, Part 4

References

1. USA Rice Federation, 2011/2012 *U.S. Rice Domestic Usage Report*

http://www.usarice.com/index.php

Figure 9.33e. Memorandum to File: Estimates of Rice Market Shares, Part 5

9.8 DETAILED EXPOSURE CALCULATIONS

9.8.1 CALCULATION OF INORGANIC ARSENIC (IAS) IN ALL BROWN RICE AND ALL WHITE RICE

Table 9.17. Calculation of iAs Concentration in All Rice, Weighted by Market Share of Individual Rice Types

Rice Type	Market Share USDA-ERS and USA Rice data (%)	Market Share Adjusted to exclude "other" (%)	iAs concentration (ppb)	Market share multiplied by iAs concentration/100 (ppb)
Brown Basmati	0.9	1.1	133.3	1.5
Brown Jasmine	0.1	0.1	142.4	0.1
Brown Instant/pre-cooked	0.2	0.2	72	0.1
Brown Parboiled	0.7	0.8	191.3	1.5
Brown Long/med/short grain, regular	3.2	3.8	156.5	5.9
White Basmati	1.8	2.1	62.3	1.3
White Jasmine	9.1	10.8	75.1	8.1
White Instant/pre-cooked	2.1	2.5	57.6	1.4
White Parboiled	8	9.5	112.4	10.7
White Long grain, regular	37.1	44	102	44.9
White Medium grain, regular	18.5	21.9	81.5	17.8
White Short grain, regular	2.6	3.1	78.9	2.4
Other	15.7	—	—	—
Sum:	100	100	—	96 ppb

Table 9.18. Calculation of iAs Concentration in Brown Rice, Weighted by Market Share of Individual Brown Rice Types

Rice Type	Market Share USDA-ERS and USA Rice data (%)	Market Share Adjusted to exclude "other" (%)	Market Share Brown rice only (%)	iAs concentration (ppb)	Market share multiplied by iAs concentration/100 (ppb)
Brown Basmati	0.9	1.1	18.3	133.3	24.4
Brown Jasmine	0.1	0.1	1.7	142.4	2.4
Brown Instant/pre-cooked	0.2	0.2	3.3	72	2.4
Brown Parboiled	0.7	0.8	13.3	191.3	25.4
Brown Long/med/short grain, regular	3.2	3.8	63.3	156.5	99.1
White Basmati	1.8	2.1	—	62.3	—
White Jasmine	9.1	10.8	—	75.1	—
White Instant/pre-cooked	2.1	2.5	—	57.6	—
White Parboiled	8	9.5	—	112.4	—
White Long grain, regular	37.1	44	—	102	—
White Medium grain, regular	18.5	21.9	—	81.5	—
White Short grain, regular	2.6	3.1	—	78.9	—
Other	15.7	—	—	—	—
Sum:	100	100	100	—	154 ppb

Table 9.19. Calculation of iAs Concentration in White Rice, Weighted by Market Share of Individual White Rice Types

Rice Type	Market Share USDA-ERS and USA Rice data (%)	Market Share Adjusted to exclude "other" (%)	Market Share White rice only (%)	iAs concentration (ppb)	Market share multiplied by iAs concentration/100 (ppb)
Brown Basmati	0.9	1.1	—	—	—
Brown Jasmine	0.1	0.1	—	—	—
Brown Instant/pre-cooked	0.2	0.2	—	—	—
Brown Parboiled	0.7	0.8	—	—	—
Brown Long/med/short grain, regular	3.2	3.8	—	—	—
White Basmati	1.8	2.1	2.2	62.3	1.4
White Jasmine	9.1	10.8	11.5	75.1	8.6
White Instant/pre-cooked	2.1	2.5	2.7	57.6	1.6
White Parboiled	8	9.5	10.1	112.4	11.4
White Long grain, regular	37.1	44	46.8	102	47.7
White Medium grain, regular	18.5	21.9	23.3	81.5	19.0
White Short grain, regular	2.6	3.1	3.3	78.9	2.6
Other	15.7	—	—	—	—
Sum:	100	100	100	—	92.3

Notes: Based on http://www.fas.usda.gov/gats/ExpressQuery1.aspx; 1.3 Brown jasmine, 98.7 White jasmine, 34.8 Brown Basmati, 65.2 White Basmati; Relative weights for brown vs. white instant and parboiled rice: PC for ages 0-50 y is 1.6 g/day and 8.5% for all brown rice, and 17.3 g/day and 91.5% for all white rice. Weghted standard errors were calculated using proc means in SAS v.9.3.

9.8.2 CALCULATION OF INTAKE OF SPECIFIC RICE TYPES

Table 9.20. Calculation of Intakes of Specific Rice Types: Market Share Multiplied by Per Capita Intake

Rice Type	Market share USDA-ERS and USA Rice data (%)	Mean per capita Intake of All Rice 0 – 6 years g/kg bw/day	Mean per capita Intake of All Rice 0 – 50 years g/kg bw/day
Brown Basmati	0.9	0.005	0.003
Brown Jasmine	0.1	0.001	0
Brown Instant/pre-cooked	0.2	0.001	0.001
Brown Parboiled	0.7	0.004	0.002
Brown Long/med/short grain, regular	3.2	0.018	0.011
White Basmati	1.8	0.01	0.006
White Jasmine	9.1	0.052	0.03
White Instant/pre-cooked	2.1	0.012	0.007
White Parboiled	8	0.045	0.027
White Long grain, regular	37.1	0.21	0.123
White Medium grain, regular	18.5	0.105	0.061
White Short grain, regular	2.6	0.015	0.009
Other	15.7	0.089	0.052
Sum:	100	0.566	0.332

9.9 NHANES/ WWEIA DATA

9.9.1 RICE-CONTAINING FOODS REPORTED BY NHANES/WWEIA RESPONDENTS

Table 9.21. NHANES/WWEIA Food Codes Containing Rice

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
11425000	Yogurt, chocolate, NS as to type of milk	1500325000	Rice, flour	0.11
11426000	Yogurt, chocolate, whole milk	1500325000	Rice, flour	0.1
11427000	Yogurt, chocolate, nonfat milk	1500325000	Rice, flour	0.11
11519000	Milk beverage, made with whole milk, flavors other than chocolate	1500325000	Rice, flour	0.03
11519040	Milk, flavors other than chocolate, NFS	1500325000	Rice, flour	0.03

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
11519050	Milk, flavors other than chocolate, whole milk-based	1500325000	Rice, flour	0.03
11519105	Milk, flavors other than chocolate, reduced fat milk-based	1500325000	Rice, flour	0.03
11519200	Milk, flavors other than chocolate, lowfat milk-based	1500325000	Rice, flour	0.03
11519205	Milk, flavors other than chocolate, skim-milk based	1500325000	Rice, flour	0.03
11525000	Milk, malted, fortified, natural flavor, made with milk	1500325000	Rice, flour	0.009
11542100	Carry-out milk shake, chocolate	1500325000	Rice, flour	0.005
11542200	Carry-out milk shake, flavors other than chocolate	1500325000	Rice, flour	0.001
11613000	Instant breakfast, powder, sweetened with low calorie sweetener, milk added	1500325000	Rice, flour	0.001
11710721	Enfamil LactoFree Lipil, with iron, infant formula, ready-to-feed	1500325001	Rice, flour-babyfood	0.02
11710900	Good Start Supreme, with iron, infant formula, NS as to form (formerly Carnation Good Start)	1500325001	Rice, flour-babyfood	0.02
11710901	Good Start Supreme, with iron, infant formula, ready-to-feed (formerly Carnation Good Start)	1500325001	Rice, flour-babyfood	0.02
11710902	Good Start Supreme, with iron, infant formula, prepared from liquid concentrate (formerly Carnation Good Start)	1500325001	Rice, flour-babyfood	0.02
11710903	Good Start Supreme, with iron, infant formula, prepared from powder (formerly Carnation Good Start)	1500325001	Rice, flour-babyfood	0.02
11710911	Good Start Supreme, with iron, DHA & ARA, infant formula, ready-to-feed	1500325001	Rice, flour-babyfood	0.02
11710912	Good Start Supreme, with iron, DHA & ARA, infant formula, prepared from liquid concentrate	1500325001	Rice, flour-babyfood	0.02
11710913	Good Start Supreme, with iron, DHA & ARA, infant formula, prepared from powder	1500325001	Rice, flour-babyfood	0.02
11830210	Milk, malted, dry mix, fortified, not reconstituted, flavors other than chocolate	1500325000	Rice, flour	0.11
11830400	Milk beverage, powder, dry mix, not reconstituted, flavors other than chocolate	1500325000	Rice, flour	0.41
11830940	Meal replacement, high protein, milk based, fruit juice mixable formula, powdered, not reconstituted	1500325000	Rice, flour	0.09
11830970	Meal replacement, protein type, milk-based, powdered, not reconstituted	1500325000	Rice, flour	0.01
11830970	Meal replacement, protein type, milk-based, powdered, not reconstituted	1500326000	Rice, bran	0.5
11835100	Meal replacement, Amway's Nutrilite brand Positrim Drink Mix, powdered nonfat dry milk-based, dry, not reconstituted	1500325000	Rice, flour	0.11
12220400	Whipped cream substitute, nondairy, lowfat, low sugar, made from powdered mix	1500325000	Rice, flour	0.13
12350100	Spinach dip	1500325000	Rice, flour	0.006
13120100	Ice cream bar or stick, chocolate covered	1500323000	Rice, white	0.001
13120100	Ice cream bar or stick, chocolate covered	1500325000	Rice, flour	0.001
13160150	Fat free ice cream, no sugar added, chocolate	1500325000	Rice, flour	0.1
13160160	Fat free ice cream, no sugar added, flavors other than chocolate	1500325000	Rice, flour	0.25
13160200	Milk dessert, frozen, lowfat, flavors other than chocolate	1500325000	Rice, flour	6.74
13160400	Fat free ice cream, flavors other than chocolate	1500325000	Rice, flour	0.002
13160410	Fat free ice cream, chocolate	1500325000	Rice, flour	0.08
13160600	Milk dessert, frozen, made with low-calorie sweetener, flavors other than chocolate	1500325000	Rice, flour	0.1
13160650	Milk dessert, frozen, made with low-calorie sweetener, chocolate	1500325000	Rice, flour	0.1
13161500	Milk dessert sandwich bar, frozen, made from lowfat milk	1500325000	Rice, flour	0.002

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
13210250	Pudding, chocolate, low calorie, containing artificial sweetener, NS as to from dry mix or ready-to-eat	1500325000	Rice, flour	0.01
13210290	Pudding, flavors other than chocolate, low calorie, containing artificial sweetener, NS as to from dry mix or ready-to-eat	1500325000	Rice, flour	0.01
13210410	Pudding, rice	1500323000	Rice, white	11.24
13210450	Pudding, rice flour, with nuts (Indian dessert)	1500323000	Rice, white	11.85
13220120	Pudding, chocolate, prepared from dry mix, milk added	1500325000	Rice, flour	0.005
13220210	Pudding, flavors other than chocolate, prepared from dry mix, low calorie, containing artificial sweetener, milk added	1500325000	Rice, flour	0.01
13220220	Pudding, chocolate, prepared from dry mix, low calorie, containing artificial sweetener, milk added	1500325000	Rice, flour	0.01
13220240	Pudding, ready-to-eat, flavors other than chocolate, reduced fat	1500325000	Rice, flour	0.1
13230110	Pudding, ready-to-eat, flavors other than chocolate	1500325000	Rice, flour	0.04
13230120	Pudding, ready-to-eat, low calorie, containing artificial sweetener, flavors other than chocolate	1500325000	Rice, flour	0.01
13230130	Pudding, ready-to-eat, chocolate	1500325000	Rice, flour	0.04
13230140	Pudding, ready-to-eat, low calorie, containing artificial sweetener, chocolate	1500325000	Rice, flour	0.01
13230200	Pudding, ready-to-eat, chocolate and non-chocolate flavors combined	1500325000	Rice, flour	0.04
13230500	Pudding, ready-to-eat, tapioca	1500325000	Rice, flour	0.005
14108060	Parmesan cheese topping, fat free	1500325000	Rice, flour	7.4
14202010	Cheese, cottage, with fruit	1500325000	Rice, flour	0.003
14410330	Cheese, processed cheese product, American or Cheddar type, reduced fat	1500325000	Rice, flour	0.98
14410340	Cheese, processed cheese product, American or Cheddar type, reduced fat, reduced sodium	1500325000	Rice, flour	0.65
14420000	Cheese spread, NFS	1500325000	Rice, flour	0.8
14420100	Cheese spread, American or Cheddar cheese base	1500325000	Rice, flour	0.8
14420160	Cheese spread, Swiss cheese base	1500325000	Rice, flour	0.8
14420300	Cheese spread, pressurized can	1500325000	Rice, flour	0.8
14502010	Imitation cheese, American or cheddar type	1500325000	Rice, flour	2.14
14502040	Imitation cheese, American or cheddar type, low cholesterol	1500325000	Rice, flour	0.18
14504010	Imitation mozzarella cheese	1500325000	Rice, flour	4.38
14620100	Dip, cream cheese base	1500325000	Rice, flour	0.002
14620120	Shrimp dip, cream cheese base	1500325000	Rice, flour	0.002
14620150	Dip, cheese with chili pepper (chili con queso)	1500325000	Rice, flour	0.56
14620200	Dip, cheese base other than cream cheese	1500325000	Rice, flour	0.8
14650160	Alfredo sauce	1500325000	Rice, flour	0.06
14710200	Beer soup, made with milk	1500323000	Rice, white	1.84
21002000	Beef, pickled	1500325000	Rice, flour	0.001
21416000	Corned beef, cooked, NS as to fat eaten	1500325000	Rice, flour	0.001
21416110	Corned beef, cooked, lean and fat eaten	1500325000	Rice, flour	0.001
21601000	Beef, bacon, cooked	1500325000	Rice, flour	0.002
21601250	Beef, bacon, cooked, lean only eaten	1500325000	Rice, flour	0.3
21601500	Beef, bacon, formed, lean meat added, cooked	1500325000	Rice, flour	0.002
21602000	Beef, dried, chipped, uncooked	1500325000	Rice, flour	0.002
21602100	Beef jerky	1500325000	Rice, flour	0.002
21603000	Beef, pastrami (beef, smoked, spiced)	1500325000	Rice, flour	0.004

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
22001000	Pork, pickled, NS as to cut	1500325000	Rice, flour	0.001
22002800	Pork jerky	1500325000	Rice, flour	0.002
22003000	Pork, dehydrated, oriental style	1500325000	Rice, flour	0.001
22300120	Ham, fried, NS as to fat eaten	1500325000	Rice, flour	0.001
22300130	Ham, fried, lean and fat eaten	1500325000	Rice, flour	0.001
22300150	Ham, breaded or floured, fried, NS as to fat eaten	1500325000	Rice, flour	0.001
22300160	Ham, breaded or floured, fried, lean and fat eaten	1500325000	Rice, flour	0.001
22311000	Ham, smoked or cured, cooked, NS as to fat eaten	1500325000	Rice, flour	0.001
22311010	Ham, smoked or cured, cooked, lean and fat eaten	1500325000	Rice, flour	0.001
22311200	Ham, smoked or cured, low sodium, cooked, NS as to fat eaten	1500325000	Rice, flour	0.001
22311210	Ham, smoked or cured, low sodium, cooked, lean and fat eaten	1500325000	Rice, flour	0.001
22311220	Ham, smoked or cured, low sodium, cooked, lean only eaten	1500325000	Rice, flour	0.001
22311450	Ham, prosciutto	1500325000	Rice, flour	0.001
22311510	Ham, smoked or cured, canned, lean and fat eaten	1500325000	Rice, flour	0.001
22321110	Ham, smoked or cured, ground patty	1500325000	Rice, flour	0.001
22421000	Pork roast, smoked or cured, cooked, NS as to fat eaten	1500325000	Rice, flour	0.001
22421010	Pork roast, smoked or cured, cooked, lean and fat eaten	1500325000	Rice, flour	0.001
22431000	Pork roll, cured, fried	1500325000	Rice, flour	0.001
22501010	Canadian bacon, cooked	1500325000	Rice, flour	0.002
22600100	Bacon, NS as to type of meat, cooked	1500325000	Rice, flour	0.001
22600200	Pork bacon, NS as to fresh, smoked or cured, cooked	1500325000	Rice, flour	0.001
22601000	Pork bacon, smoked or cured, cooked	1500325000	Rice, flour	0.001
22601020	Pork bacon, smoked or cured, cooked, lean only eaten	1500325000	Rice, flour	0.002
22601040	Bacon or side pork, fresh, cooked	1500325000	Rice, flour	0.001
22602010	Pork bacon, smoked or cured, lower sodium	1500325000	Rice, flour	0.001
22605010	Pork bacon, formed, lean meat added, cooked	1500325000	Rice, flour	0.001
22707020	Pork, pig's feet, pickled	1500325000	Rice, flour	0.001
22708010	Pork, pig's hocks, cooked	1500325000	Rice, flour	0.001
23345100	Wild pig, smoked	1500325000	Rice, flour	0.001
24198570	Chicken, canned, meat only	1500325000	Rice, flour	0.001
24204000	Turkey, rolled roast, light or dark meat, cooked	1500325000	Rice, flour	0.004
25220010	Cold cut, NFS	1500325000	Rice, flour	0.001
25220210	Blood sausage	1500325000	Rice, flour	0.002
25220350	Bratwurst, pork, cooked	1500325000	Rice, flour	0.003
25220360	Bratwurst, with cheese	1500325000	Rice, flour	0.002
25220370	Bratwurst, beef, cooked	1500325000	Rice, flour	0.003
25220410	Bologna, NFS	1500325000	Rice, flour	0.003
25220450	Bologna ring, smoked	1500325000	Rice, flour	0.003
25220480	Bologna, chicken, beef, and pork	1500325000	Rice, flour	0.001
25220490	Bologna, with cheese	1500325000	Rice, flour	0.003
25220500	Bologna, beef and pork, lowfat	1500325000	Rice, flour	0.002
25221400	Sausage (not cold cut), NFS	1500325000	Rice, flour	0.001
25221410	Pork sausage, fresh, bulk, patty or link, cooked	1500325000	Rice, flour	0.001
25221420	Pork sausage, brown and serve, cooked	1500325000	Rice, flour	0.001
25221430	Pork sausage, country style, fresh, cooked	1500325000	Rice, flour	0.001
25221450	Pork sausage rice links, brown and serve, cooked	1500323000	Rice, white	3.58
25221860	Turkey sausage, reduced fat, brown and serve, cooked	1500325000	Rice, flour	0.001
25221870	Turkey and pork sausage, fresh, bulk, patty or link, cooked	1500325000	Rice, flour	0.001

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
25230210	Ham, sliced, prepackaged or deli, luncheon meat	1500325000	Rice, flour	0.001
25230220	Ham, sliced, low salt, prepackaged or deli, luncheon meat	1500325000	Rice, flour	0.001
25230610	Luncheon loaf (olive, pickle, or pimiento)	1500325000	Rice, flour	0.05
25240110	Chicken salad spread	1500325000	Rice, flour	0.08
25240220	Ham salad spread	1500325000	Rice, flour	0.002
25240310	Roast beef spread	1500325000	Rice, flour	0.004
27113200	Creamed chipped or dried beef	1500325000	Rice, flour	0.001
27118110	Meatballs, Puerto Rican style (Albondigas guisadas)	1500325000	Rice, flour	0.001
27118130	Stewed dried beef, Puerto Rican style (Tasajo guisado, carne cecina guisada)	1500325000	Rice, flour	0.001
27118180	Puerto Rican style beef stew, meat with gravy (potatoes reported separately)	1500325000	Rice, flour	0.01
27120020	Ham or pork with gravy (mixture)	1500325000	Rice, flour	0.001
27120030	Ham or pork with barbecue sauce (mixture)	1500325000	Rice, flour	0.001
27120090	Ham or pork with (mushroom) soup (mixture)	1500325000	Rice, flour	0.001
27120100	Ham or pork with tomato-based sauce (mixture)	1500325000	Rice, flour	0.001
27120110	Sausage with tomato-based sauce (mixture)	1500325000	Rice, flour	0.001
27120120	Sausage gravy	1500325000	Rice, flour	0.001
27120150	Pork or ham with soy-based sauce (mixture)	1500325000	Rice, flour	0.001
27120210	Frankfurter or hot dog, with chili, no bun	1500325000	Rice, flour	0.01
27121010	Stewed pork, Puerto Rican style	1500325000	Rice, flour	0.001
27133010	Stewed goat, Puerto Rican style (Cabrito en fricase, chilindron de chivo)	1500325000	Rice, flour	0.001
27146250	Chicken or turkey cordon bleu	1500325000	Rice, flour	0.001
27162010	Meat with tomato-based sauce (mixture)	1500325000	Rice, flour	0.01
27163010	Meat with gravy, NS as to type of meat (mixture)	1500325000	Rice, flour	0.001
27211400	Corned beef hash	1500325000	Rice, flour	0.001
27213000	Beef and rice, no sauce (mixture)	1500323000	Rice, white	23.49
27213100	Beef and rice with tomato-based sauce (mixture)	1500323000	Rice, white	11.39
27213120	Porcupine balls with tomato-based sauce (mixture)	1500323000	Rice, white	9.69
27213150	Chili con carne with beans and rice	1500323000	Rice, white	13.62
27213150	Chili con carne with beans and rice	1500325000	Rice, flour	0.01
27213200	Beef and rice with gravy (mixture)	1500323000	Rice, white	14.43
27213300	Beef and rice with cream sauce (mixture)	1500323000	Rice, white	14.03
27213400	Beef and rice with (mushroom) soup (mixture)	1500323000	Rice, white	10.98
27213420	Porcupine balls with (mushroom) soup (mixture)	1500323000	Rice, white	9.74
27213500	Beef and rice with soy-based sauce (mixture)	1500323000	Rice, white	7.58
27213600	Beef and rice with cheese sauce (mixture)	1500323000	Rice, white	15.03
27214500	Corned beef patty	1500325000	Rice, flour	0.001
27218210	Puerto Rican style beef stew with potatoes (Carne guisada con papas)	1500325000	Rice, flour	6.6E-05
27218310	Stewed corned beef, Puerto Rican style ("Corned beef" guisado)	1500325000	Rice, flour	0.001
27220010	Meat loaf made with ham (not luncheon meat)	1500325000	Rice, flour	0.001
27220030	Ham and rice with (mushroom) soup (mixture)	1500323000	Rice, white	10.25
27220050	Ham or pork with stuffing (mixture)	1500325000	Rice, flour	0.001
27220110	Pork and rice with tomato-based sauce (mixture)	1500323000	Rice, white	15.97
27220120	Sausage and rice with tomato-based sauce (mixture)	1500323000	Rice, white	16.48
27220120	Sausage and rice with tomato-based sauce (mixture)	1500325000	Rice, flour	0.001
27220150	Sausage and rice with (mushroom) soup (mixture)	1500323000	Rice, white	11.8

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
27220150	Sausage and rice with (mushroom) soup (mixture)	1500325000	Rice, flour	0.001
27220170	Sausage and rice with cheese sauce (mixture)	1500323000	Rice, white	13.03
27220190	Sausage and noodles with cream or white sauce (mixture)	1500325000	Rice, flour	0.001
27220310	Ham or pork and rice, no sauce (mixture)	1500323000	Rice, white	22.03
27220310	Ham or pork and rice, no sauce (mixture)	1500325000	Rice, flour	0.001
27220510	Ham or pork and potatoes with gravy (mixture)	1500325000	Rice, flour	0.001
27220520	Ham or pork and potatoes with cheese sauce (mixture)	1500325000	Rice, flour	0.001
27243000	Chicken or turkey and rice, no sauce (mixture)	1500323000	Rice, white	22.06
27243300	Chicken or turkey and rice with cream sauce (mixture)	1500323000	Rice, white	11.51
27243400	Chicken or turkey and rice with (mushroom) soup (mixture)	1500323000	Rice, white	13.06
27243500	Chicken or turkey and rice with tomato-based sauce (mixture)	1500323000	Rice, white	10.7
27243600	Chicken or turkey and rice with soy-based sauce (mixture)	1500323000	Rice, white	4.9
27243700	Chicken in cheese sauce with Spanish rice	1500323000	Rice, white	14.68
27250124	Shrimp and noodles with (mushroom) soup (mixture)	1500325000	Rice, flour	0.02
27250270	Clams Casino	1500325000	Rice, flour	0.001
27250710	Tuna and rice with (mushroom) soup (mixture)	1500323000	Rice, white	10.82
27250810	Fish and rice with tomato-based sauce	1500323000	Rice, white	11.04
27250820	Fish and rice with cream sauce	1500323000	Rice, white	14.03
27250830	Fish and rice with (mushroom) soup	1500323000	Rice, white	11.04
27260110	Hash, NS as to type of meat	1500325000	Rice, flour	0.001
27260500	Vienna sausages stewed with potatoes, Puerto Rican style (Salchichas guisadas)	1500325000	Rice, flour	0.001
27311210	Corned beef, potatoes, and vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce (mixture)	1500325000	Rice, flour	0.001
27311220	Corned beef, potatoes, and vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce (mixture)	1500325000	Rice, flour	0.001
27315010	Beef, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce (mixture)	1500323000	Rice, white	12.33
27315020	Beef, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce (mixture)	1500323000	Rice, white	12.38
27315210	Beef, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), tomato-based sauce (mixture)	1500323000	Rice, white	8.05
27315220	Beef, rice, and vegetables (excluding carrots, broccoli, and/or dark-green leafy), tomato-based sauce (mixture)	1500323000	Rice, white	7.49
27315250	Stuffed cabbage rolls with beef and rice	1500323000	Rice, white	4.45
27315270	Stuffed grape leaves with beef and rice	1500323000	Rice, white	6.58
27315310	Beef, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), (mushroom) soup (mixture)	1500323000	Rice, white	10.46
27315320	Beef, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), (mushroom) soup (mixture)	1500323000	Rice, white	10.52
27315340	Beef, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), cheese sauce (mixture)	1500323000	Rice, white	11.07
27315410	Beef, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), gravy (mixture)	1500323000	Rice, white	7.5
27315420	Beef, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), gravy (mixture)	1500323000	Rice, white	7.02
27315510	Beef, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), soy-based sauce (mixture)	1500323000	Rice, white	7.71

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27315520	Beef, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), soy-based sauce (mixture)	1500323000	Rice, white	8.38
27320320	Pork, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), soy-based sauce (mixture)	1500323000	Rice, white	10.18
27320330	Pork, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), soy-based sauce (mixture)	1500323000	Rice, white	9.98
27320340	Pork, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), tomato-based sauce (mixture)	1500323000	Rice, white	8.05
27320350	Pork, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), tomato-based sauce (mixture)	1500323000	Rice, white	9.31
27320500	Sweet and sour pork with rice	1500323000	Rice, white	11.28
27330050	Lamb or mutton, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), gravy (mixture)	1500323000	Rice, white	29.62
27330060	Lamb or mutton, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), tomato-based sauce (mixture)	1500323000	Rice, white	8.88
27330080	Lamb or mutton, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), gravy	1500323000	Rice, white	8.88
27330170	Stuffed grape leaves with lamb and rice	1500323000	Rice, white	7.13
27331150	Veal fricassee, Puerto Rican style (ternera en fricase)	1500325000	Rice, flour	0.001
27341040	Chicken or turkey, potatoes, and vegetables (excluding carrots, broccoli, and dark-green leafy), cream sauce, white sauce, or mushroom soup-based sauce (mixture)	1500325000	Rice, flour	0.006
27345010	Chicken or turkey, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce (mixture)	1500323000	Rice, white	13.32
27345020	Chicken or turkey, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce (mixture)	1500323000	Rice, white	11.68
27345210	Chicken or turkey, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), gravy (mixture)	1500323000	Rice, white	11.31
27345220	Chicken or turkey, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), gravy (mixture)	1500323000	Rice, white	12.04
27345310	Chicken or turkey, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), soy-based sauce (mixture)	1500323000	Rice, white	7.89
27345320	Chicken or turkey, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), soy-based sauce (mixture)	1500323000	Rice, white	7.88
27345410	Chicken or turkey, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), cream sauce, white sauce, or mushroom soup-based sauce (mixture)	1500323000	Rice, white	10.91
27345420	Chicken or turkey, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), cream sauce, white sauce, or mushroom soup-based sauce (mixture)	1500323000	Rice, white	10.89
27345440	Chicken or turkey, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), cheese sauce (mixture)	1500323000	Rice, white	7.67
27345450	Chicken or turkey, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), cheese sauce (mixture)	1500323000	Rice, white	10.3
27345510	Chicken or turkey, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy), tomato-based sauce (mixture)	1500323000	Rice, white	12.47
27345520	Chicken or turkey, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy), tomato-based sauce (mixture)	1500323000	Rice, white	12
27348100	Chicken fricassee, Puerto Rican style (Fricase de pollo)	1500325000	Rice, flour	0.001
27350020	Paella with seafood	1500323000	Rice, white	18.16

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27350030	Seafood stew with potatoes and vegetables (excluding carrots, broccoli, and dark-green leafy), tomato-base sauce	1500325000	Rice, flour	0.001
27350060	Shrimp creole, with rice	1500323000	Rice, white	10.15
27350310	Seafood stew with potatoes and vegetables (including carrots, broccoli, and/or dark-green leafy), tomato-base sauce	1500325000	Rice, flour	0.001
27360090	Paella, NFS	1500323000	Rice, white	16.66
27360120	Chow mein or chop suey, various types of meat, with noodles	1500325000	Rice, flour	0.001
27361010	Stewed variety meats, Puerto Rican style (mostly liver) (Gandinga)	1500325000	Rice, flour	0.001
27362000	Stewed tripe, Puerto Rican style, with potatoes (Mondongo)	1500325000	Rice, flour	0.001
27363000	Gumbo with rice (New Orleans type with shellfish, pork, and/or poultry, tomatoes, okra, rice)	1500323000	Rice, white	3.79
27363100	Jambalaya with meat and rice	1500323000	Rice, white	9.66
27363100	Jambalaya with meat and rice	1500325000	Rice, flour	0.001
27420020	Ham or pork salad	1500325000	Rice, flour	0.001
27420080	Greens with ham or pork (mixture)	1500325000	Rice, flour	0.001
27420450	Sausage and vegetables (including carrots, broccoli, and/or dark-green leafy (no potatoes)), tomato-based sauce (mixture)	1500325000	Rice, flour	0.001
27420460	Sausage and vegetables (excluding carrots, broccoli, and dark-green leafy (no potatoes)), tomato-based sauce (mixture)	1500325000	Rice, flour	0.001
27421010	Stuffed christophine, Puerto Rican style (Chayote relleno)	1500325000	Rice, flour	0.24
27446205	Chicken or turkey salad with nuts and/or fruits	1500325000	Rice, flour	0.08
27446315	Chicken or turkey garden salad with bacon (chicken and/or turkey, bacon, cheese, lettuce and/or greens, tomato and/or carrots, other vegetables), no dressing	1500325000	Rice, flour	0.001
27446320	Chicken or turkey (breaded, fried) garden salad with bacon (chicken and/or turkey, bacon, cheese, lettuce and/or greens, tomato and/or carrots, other vegetables), no dressing	1500325000	Rice, flour	0
27450010	Crab salad	1500325000	Rice, flour	0.004
27450020	Lobster salad	1500325000	Rice, flour	0.002
27450060	Tuna salad	1500325000	Rice, flour	0.003
27450090	Tuna salad with cheese	1500325000	Rice, flour	0.003
27450100	Tuna salad with egg	1500325000	Rice, flour	0.003
27450130	Crab salad made with imitation crab	1500325000	Rice, flour	0.004
27500050	Sandwich, NFS	1500325000	Rice, flour	0.001
27500100	Meat sandwich, NFS	1500325000	Rice, flour	0.001
27510360	Bacon cheeseburger, with mayonnaise or salad dressing, tomato and/or catsup, on bun	1500325000	Rice, flour	0.001
27510390	Double bacon cheeseburger (2 patties, 1/4 lb meat each), on bun	1500325000	Rice, flour	0.001
27510400	Bacon cheeseburger, 1/4 lb meat, with tomato and/or catsup, on bun	1500325000	Rice, flour	0.001
27510425	Double bacon cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing, on bun	1500325000	Rice, flour	0.001
27510430	Double bacon cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing, and tomato and/or catsup, on bun	1500325000	Rice, flour	0.001
27510435	Double bacon cheeseburger (2 patties,1/3 lb meat each), with mayonnaise or salad dressing, on bun	1500325000	Rice, flour	0.001
27510440	Bacon cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing, and tomato and/or catsup, on bun	1500325000	Rice, flour	0.001
27510450	Cheeseburger, 1/4 lb meat, with ham, on bun	1500325000	Rice, flour	0.001
27510700	Meatball and spaghetti sauce submarine sandwich	1500325000	Rice, flour	0.006

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27510950	Reuben sandwich (corned beef sandwich with sauerkraut and cheese), with spread	1500325000	Rice, flour	0.001
27511010	Pastrami sandwich	1500325000	Rice, flour	0.03
27513060	Roast beef sandwich with bacon and cheese sauce	1500325000	Rice, flour	0.001
27516010	Gyro sandwich (pita bread, beef, lamb, onion, condiments), with tomato and spread	1500325000	Rice, flour	0.001
27520120	Bacon and cheese sandwich, with spread	1500325000	Rice, flour	0.001
27520130	Bacon, chicken, and tomato club sandwich, with lettuce and spread	1500325000	Rice, flour	0.001
27520135	Bacon, chicken, and tomato club sandwich, with cheese, lettuce and spread	1500325000	Rice, flour	0.001
27520140	Bacon and egg sandwich	1500325000	Rice, flour	0.001
27520150	Bacon, lettuce, and tomato sandwich with spread	1500325000	Rice, flour	0.001
27520160	Bacon, chicken, and tomato club sandwich, on multigrain roll with lettuce and spread	1500325000	Rice, flour	0.001
27520165	Bacon, chicken fillet (breaded, fried), and tomato club with lettuce and spread	1500325000	Rice, flour	0
27520166	Bacon, chicken fillet (breaded, fried), and tomato club sandwich with cheese, lettuce and spread	1500325000	Rice, flour	0
27520170	Bacon on biscuit	1500325000	Rice, flour	0.001
27520330	Ham and egg sandwich	1500325000	Rice, flour	0.001
27520540	Ham and tomato club sandwich, with lettuce and spread	1500325000	Rice, flour	0.001
27540235	Chicken fillet, broiled, sandwich with lettuce, tomato, and spread	1500325000	Rice, flour	0.001
27540240	Chicken fillet, (broiled), sandwich, on whole wheat roll, with lettuce, tomato and spread	1500325000	Rice, flour	0.001
27540270	Chicken fillet, broiled, sandwich, with lettuce, tomato, and non-mayonnaise type spread	1500325000	Rice, flour	0.009
27550000	Fish sandwich, on bun, with spread	1500325000	Rice, flour	0.002
27550100	Fish sandwich, on bun, with cheese and spread	1500325000	Rice, flour	0.001
27550710	Tuna salad sandwich, with lettuce	1500325000	Rice, flour	0.002
27550720	Tuna salad sandwich	1500325000	Rice, flour	0.002
27550750	Tuna salad submarine sandwich, with lettuce and tomato	1500325000	Rice, flour	0.002
27550751	Tuna salad submarine sandwich, with cheese, lettuce and tomato	1500325000	Rice, flour	0.002
27560110	Bologna sandwich, with spread	1500325000	Rice, flour	0.001
27560120	Bologna and cheese sandwich, with spread	1500325000	Rice, flour	0.001
27560360	Frankfurter or hot dog, with chili, on bun	1500325000	Rice, flour	0.01
27560370	Frankfurter or hot dog with chili and cheese, on bun	1500325000	Rice, flour	0.005
27560705	Sausage balls (made with biscuit mix and cheese)	1500325000	Rice, flour	0.001
27560910	Cold cut submarine sandwich, with cheese, lettuce, tomato, and spread	1500325000	Rice, flour	0.002
27563010	Meat spread or potted meat sandwich	1500325000	Rice, flour	0.002
27570310	Hors d'oeuvres, with spread	1500325000	Rice, flour	0.002
27610100	Beef and egg noodles, baby food, NS as to strained or junior	1500325001	Rice, flour-babyfood	3.5
27610100	Beef and egg noodles, baby food, NS as to strained or junior	1500326001	Rice, bran-babyfood	0.05
27610110	Beef and egg noodles, baby food, strained	1500326001	Rice, bran-babyfood	0.1
27610120	Beef and egg noodles, baby food, junior	1500325001	Rice, flour-babyfood	7
27640050	Chicken and rice dinner, baby food, strained	1500323001	Rice, white-babyfood	8
27640100	Chicken noodle dinner, baby food, NS as to strained or junior	1500325001	Rice, flour-babyfood	6.3
27640110	Chicken noodle dinner, baby food, strained	1500325001	Rice, flour-babyfood	7.6
27640120	Chicken noodle dinner, baby food, junior	1500325001	Rice, flour-babyfood	5

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27642100	Turkey, rice and vegetables, baby food, NS as to strained or junior	1500323001	Rice, white-babyfood	4.5
27642110	Turkey, rice and vegetables, baby food, strained	1500325001	Rice, flour-babyfood	5
27642120	Turkey, rice and vegetables, baby food, junior	1500323001	Rice, white-babyfood	5
27642130	Turkey, rice, and vegetables, baby food, toddler	1500324001	Rice, brown-babyfood	7
27644110	Chicken soup, baby food	1500323001	Rice, white-babyfood	6
27644110	Chicken soup, baby food	1500326001	Rice, bran-babyfood	0.1
28110260	Sirloin tips, potato, vegetable, fruit (diet frozen meal)	1500325000	Rice, flour	0.03
28110290	Sirloin tips and mushrooms in wine sauce with rotini (diet frozen entree)	1500325000	Rice, flour	0.01
28110390	Salisbury steak, potatoes, vegetable, dessert (diet frozen meal)	1500325000	Rice, flour	0.003
28110500	Beef, sliced, with gravy, barley and wild rice, vegetables (diet frozen meal)	1500325000	Rice, flour	0.002
28110650	Meatballs, Swedish, in sauce, with noodles and vegetable medley (frozen meal)	1500325000	Rice, flour	0.04
28113040	Beef, oriental style, with vegetable, rice, and fruit dessert (diet frozen meal)	1500323000	Rice, white	5.2
28113040	Beef, oriental style, with vegetable, rice, and fruit dessert (diet frozen meal)	1500325000	Rice, flour	0.006
28113140	Beef with spaetzle or rice, vegetable (frozen meal)	1500323000	Rice, white	7.26
28113150	Beef steak with rice, vegetable (diet frozen meal)	1500323000	Rice, white	7.24
28120310	Pork with rice, vegetable, in soy-based sauce (diet frozen meal)	1500323000	Rice, white	6.42
28140250	Chicken, boneless, with gravy, dressing, rice, vegetable, dessert (frozen meal, large meat portion)	1500323000	Rice, white	5.67
28140720	Chicken patty, or nuggets, boneless, breaded, potatoes, vegetable (frozen meal)	1500325000	Rice, flour	2
28140740	Chicken patty, or nuggets, boneless, breaded, with pasta and tomato sauce, fruit, dessert (frozen meal)	1500325000	Rice, flour	0.005
28141200	Chicken teriyaki with rice, vegetable (frozen meal)	1500323000	Rice, white	8.95
28141201	Teriyaki chicken with rice and vegetable (diet frozen meal)	1500323000	Rice, white	11.95
28141210	Chicken, fried in honey sauce, with Oriental style rice and vegetables, in soy-based sauce (frozen meal)	1500323000	Rice, white	12.91
28141250	Chicken with rice-vegetable mixture (diet frozen meal)	1500323000	Rice, white	8.91
28141300	Chicken with rice and vegetable, reduced fat and sodium (diet frozen meal)	1500323000	Rice, white	7.87
28141300	Chicken with rice and vegetable, reduced fat and sodium (diet frozen meal)	1500325000	Rice, flour	0.001
28141600	Chicken a la king with rice (frozen meal)	1500323000	Rice, white	14.13
28141650	Chicken and vegetables au gratin with rice-vegetable mixture (diet frozen entree)	1500323000	Rice, white	5.05
28142000	Chicken in cream sauce, with brown and wild rice, vegetable, and fruit dessert (diet frozen meal)	1500324000	Rice, brown	4.32
28142000	Chicken in cream sauce, with brown and wild rice, vegetable, and fruit dessert (diet frozen meal)	1500325000	Rice, flour	0.01
28143010	Chicken and vegetable entree with rice, Oriental (frozen meal)	1500323000	Rice, white	9.57
28143020	Chicken and vegetable entree with rice, Oriental (diet frozen meal)	1500323000	Rice, white	10.92
28143040	Chicken chow mein with rice (diet frozen meal)	1500323000	Rice, white	9.51

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28143050	Chicken chow mein with rice, reduced fat and sodium (diet frozen meal)	1500323000	Rice, white	5.95
28143050	Chicken chow mein with rice, reduced fat and sodium (diet frozen meal)	1500325000	Rice, flour	0.05
28143080	Chicken with noodles and cheese sauce (diet frozen meal)	1500325000	Rice, flour	0.004
28143190	Chicken in mushroom sauce, white and wild rice, vegetable (frozen meal)	1500323000	Rice, white	6.33
28143200	Chicken in soy-based sauce, rice and vegetables (frozen meal)	1500323000	Rice, white	6.42
28143210	Chicken in orange sauce with almond rice (diet frozen meal)	1500323000	Rice, white	13.03
28143220	Chicken in barbecue sauce, with rice, vegetable and dessert, reduced fat and sodium (diet frozen meal)	1500323000	Rice, white	6.52
28143220	Chicken in barbecue sauce, with rice, vegetable and dessert, reduced fat and sodium (diet frozen meal)	1500325000	Rice, flour	0.01
28145010	Turkey with dressing, gravy, potato (frozen meal)	1500325000	Rice, flour	0.001
28145100	Turkey with dressing, gravy, vegetable and fruit (diet frozen meal)	1500325000	Rice, flour	0.002
28145110	Turkey with vegetable, stuffing (diet frozen meal)	1500325000	Rice, flour	0.03
28145810	Turkey breast with gravy, long-grain and wild rice, vegetable (frozen meal)	1500323000	Rice, white	8.15
28145810	Turkey breast with gravy, long-grain and wild rice, vegetable (frozen meal)	1500324000	Rice, brown	0.89
28145810	Turkey breast with gravy, long-grain and wild rice, vegetable (frozen meal)	1500325000	Rice, flour	0.001
28150510	Fish in lemon-butter sauce with starch item, vegetable (frozen meal)	1500323000	Rice, white	8.55
28152030	Seafood newburg with rice, vegetable (frozen meal)	1500323000	Rice, white	6.99
28152050	Shrimp with rice, vegetable (frozen meal)	1500323000	Rice, white	7.76
28160650	Stuffed green pepper (frozen meal)	1500323000	Rice, white	4.08
28160710	Stuffed cabbage, with meat and tomato sauce (diet frozen meal)	1500323000	Rice, white	3.11
28310230	Meatball soup, Mexican style (Sopa de Albondigas)	1500323000	Rice, white	0.57
28310330	Beef and rice noodle soup, Oriental style (Vietnamese Pho Bo)	1500325000	Rice, flour	7.6
28310420	Beef and rice soup, Puerto Rican style	1500323000	Rice, white	0.21
28315130	Beef vegetable soup with rice, stew type, chunky style	1500323000	Rice, white	2.71
28315150	Meat and corn hominy soup, Mexican style (Pozole)	1500325000	Rice, flour	0.001
28320110	Pork and rice soup, stew type, chunky style	1500323000	Rice, white	3
28320130	Ham, rice, and potato soup, Puerto Rican style	1500323000	Rice, white	2.84
28321130	Bacon soup, cream of, prepared with water	1500325000	Rice, flour	0.001
28340210	Chicken rice soup, Puerto Rican style (Sopa de pollo con arroz)	1500323000	Rice, white	2.53
28340210	Chicken rice soup, Puerto Rican style (Sopa de pollo con arroz)	1500325000	Rice, flour	0.001
28340220	Chicken soup with noodles and potatoes, Puerto Rican style	1500325000	Rice, flour	0.001
28340310	Chicken gumbo soup	1500323000	Rice, white	1.07
28340630	Chicken vegetable soup with rice, stew type, chunky style	1500323000	Rice, white	4.15
28340670	Chicken vegetable soup with rice, Mexican style (Sopa / Caldo de Pollo)	1500323000	Rice, white	1.69
28350050	Fish chowder	1500325000	Rice, flour	0.001
28350210	Clam chowder, NS as to Manhattan or New England style	1500325000	Rice, flour	0.005
28350220	Clam chowder, Manhattan	1500325000	Rice, flour	0.01
28355140	Clam chowder, New England, canned, reduced sodium, ready-to-serve	1500325000	Rice, flour	0.55
28355260	Lobster gumbo	1500323000	Rice, white	4.62
28355410	Shrimp soup, cream of, NS as to prepared with milk or water	1500325000	Rice, flour	0.02
28355430	Shrimp soup, cream of, prepared with water	1500325000	Rice, flour	0.02

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28355440	Shrimp gumbo	1500323000	Rice, white	4.24
28500150	Gravy, redeye	1500325000	Rice, flour	0.001
32105030	Egg omelet or scrambled egg, with ham or bacon	1500325000	Rice, flour	0.001
32105080	Egg omelet or scrambled egg, with ham or bacon and cheese	1500325000	Rice, flour	0.001
32105081	Egg omelet or scrambled egg, with ham or bacon, cheese, and dark-green vegetables	1500325000	Rice, flour	0.001
32105082	Egg omelet or scrambled egg, with ham or bacon, cheese, and vegetables other than dark-green	1500325000	Rice, flour	0.001
32105085	Egg omelet or scrambled egg, with ham or bacon, cheese, and tomatoes	1500325000	Rice, flour	0.001
32105118	Egg omelet or scrambled egg, with sausage and vegetables other than dark-green	1500325000	Rice, flour	0.001
32105119	Egg omelet or scrambled egg, with sausage, cheese, and vegetables other than dark-green	1500325000	Rice, flour	0.001
32105120	Egg omelet or scrambled egg, with sausage and mushrooms	1500325000	Rice, flour	0.001
32105121	Egg omelet or scrambled egg, with sausage and cheese	1500325000	Rice, flour	0.001
32105122	Egg omelet or scrambled egg, with sausage	1500325000	Rice, flour	0.001
32105190	Egg casserole with bread, cheese, milk and meat	1500325000	Rice, flour	0.001
32202010	Egg, cheese, and ham on English muffin	1500325000	Rice, flour	0.001
32202025	Egg, cheese and ham on bagel	1500325000	Rice, flour	0.001
32202035	Egg, extra cheese (2 slices), and extra sausage (2 patties) on bun	1500325000	Rice, flour	0
32202050	Egg, cheese, and sausage on biscuit	1500325000	Rice, flour	0.001
32202070	Egg, cheese, and bacon on biscuit	1500325000	Rice, flour	0.001
32202075	Egg, cheese, and bacon griddle cake sandwich	1500325000	Rice, flour	0.001
32202080	Egg, cheese, and bacon on English muffin	1500325000	Rice, flour	0.001
32202085	Egg, cheese and bacon on bagel	1500325000	Rice, flour	0.001
32202090	Egg and bacon on biscuit	1500325000	Rice, flour	0.001
33201110	Scrambled egg, made from cholesterol-free frozen mixture with cheese	1500325000	Rice, flour	0.17
35001000	Scrambled eggs, sausage, hash brown potatoes (frozen meal)	1500325000	Rice, flour	0.001
35002000	Scrambled eggs, bacon, home fried potatoes (frozen meal)	1500325000	Rice, flour	0.001
41201020	Baked beans, vegetarian	1500325000	Rice, flour	0.01
41202020	Chili beans, barbecue beans, ranch style beans or Mexican- style beans	1500325000	Rice, flour	0.02
41210090	Stewed beans with pork, tomatoes, and chili peppers, Mexican style (Frijoles a la charra)	1500325000	Rice, flour	0.001
41210100	Stewed red beans, Puerto Rican style (Habichuelas coloradas guisadas)	1500325000	Rice, flour	0.001
41210110	Stewed dry lima beans, Puerto Rican style	1500325000	Rice, flour	0.001
41210150	Stewed pink beans with white potatoes and ham, Puerto Rican style	1500325000	Rice, flour	3.8E-05
41210190	Stewed red beans with pig's feet and potatoes, Puerto Rican style	1500325000	Rice, flour	5.8E-05
41310100	Stewed pigeon peas, Puerto Rican style (Gandules guisados, Gandur, Gandules)	1500325000	Rice, flour	0.001
41310200	Chickpeas stewed with pig's feet, Puerto Rican style (Garbanzos guisados con patitas de cerdo)	1500325000	Rice, flour	0.001
41310220	Fried chickpeas with bacon, Puerto Rican style (Garbanzos fritos con tocineta)	1500325000	Rice, flour	0.001
41410015	Soy chips	1500324000	Rice, brown	26.26
41420100	Miso sauce	1500325000	Rice, flour	0.67
41420110	Miso (fermented soybean paste)	1500325000	Rice, flour	1.5

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
41420250	Hoisin sauce	1500325000	Rice, flour	0.91
41430200	Meal replacement or supplement, soy- and milk-base, powder, reconstituted with water	1500325000	Rice, flour	0.08
41435010	High protein bar, soy base	1500324000	Rice, brown	4.5
41435110	High protein bar, candy-like, soy and milk base	1500324000	Rice, brown	3.5
41435120	Zone Perfect Classic Crunch nutrition bar	1500324000	Rice, brown	5.83
41435120	Zone Perfect Classic Crunch nutrition bar	1500325000	Rice, flour	0.13
41435300	Balance Original Bar	1500324000	Rice, brown	5.83
41435300	Balance Original Bar	1500325000	Rice, flour	0.13
41435500	Clif Bar	1500324000	Rice, brown	5.83
41435500	Clif Bar	1500325000	Rice, flour	0.13
41435700	South Beach Living High Protein Cereal Bar	1500324000	Rice, brown	5.83
41435700	South Beach Living High Protein Cereal Bar	1500325000	Rice, flour	0.13
41435710	South Beach Living Meal Replacement Bar	1500324000	Rice, brown	5.83
41435710	South Beach Living Meal Replacement Bar	1500325000	Rice, flour	0.13
41440100	Meal replacement or supplement, liquid, soy-based	1500325000	Rice, flour	0.17
41501000	Mexican dinner with fried beans, frozen	1500323000	Rice, white	6.85
41601010	Bean soup, NFS	1500325000	Rice, flour	0.001
41601020	Bean with bacon or pork soup	1500325000	Rice, flour	0.001
41601070	Soybean soup, miso broth	1500325000	Rice, flour	0.07
41601100	Portuguese bean soup	1500325000	Rice, flour	0.001
41601120	Bean soup with vegetables, rice, and pork	1500323000	Rice, white	2.77
41601120	Bean soup with vegetables, rice, and pork	1500325000	Rice, flour	0.001
41601150	Bean soup with vegetables and rice, canned, reduced sodium, prepared with water or ready-to-serve	1500323000	Rice, white	4.3
41601170	Bean and rice soup	1500323000	Rice, white	4.2
41602010	Pea and ham soup, chunky style, canned or ready-to-serve	1500325000	Rice, flour	0.001
41602030	Split pea and ham soup	1500325000	Rice, flour	0.001
41602070	Split pea soup, canned, reduced sodium, prepared with water or ready-to-serve	1500325000	Rice, flour	0.001
41610100	White bean soup, Puerto Rican style (Sopon de habichuelas blancas)	1500323000	Rice, white	8.35
41810400	Breakfast link, pattie, or slice, meatless	1500325000	Rice, flour	0.003
41811400	Frankfurter or hot dog, meatless	1500325000	Rice, flour	0.001
41811600	Luncheon slice, meatless-beef, chicken, salami or turkey	1500325000	Rice, flour	0.001
41811890	Vegetarian burger or patty, meatless, no bun	1500324000	Rice, brown	3.6
41811910	Vegetable burger or patty, meatless, no bun	1500324000	Rice, brown	3.6
41812600	Vegetarian, fillet	1500324000	Rice, brown	3.6
41812850	Vegetarian stroganoff (made with meat substitute)	1500325000	Rice, flour	0.02
41812900	Vegetarian meat loaf or patties (meat loaf made with meat substitute)	1500325000	Rice, flour	0.5
51806010	Bread, rice	1500324000	Rice, brown	2.71
51806010	Bread, rice	1500326000	Rice, bran	3.26
51806020	Bread, rice, toasted	1500324000	Rice, brown	2.71
51806020	Bread, rice, toasted	1500326000	Rice, bran	3.26
51808000	Bread, low gluten	1500324000	Rice, brown	2.21
51808000	Bread, low gluten	1500326000	Rice, bran	3.26
51808010	Bread, low gluten, toasted	1500324000	Rice, brown	2.21
51808010	Bread, low gluten, toasted	1500326000	Rice, bran	3.26

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53104950	Cake, chocolate, made with mayonnaise or salad dressing, with icing, coating, or filling	1500325000	Rice, flour	0.003
53116600	Cake, rice flour, without icing	1500325000	Rice, flour	36.71
53206500	Cookie, chocolate, made with rice cereal	1500325000	Rice, flour	11.93
53226500	Cookie, marshmallow, with rice cereal (no-bake)	1500325000	Rice, flour	26.51
53226550	Cookie, marshmallow, with rice cereal and chocolate chips	1500325000	Rice, flour	39.1
53226600	Cookie, marshmallow and peanut butter, with oat cereal (no-bake)	1500325000	Rice, flour	0.01
53233020	Cookie, oatmeal, with fruit filling	1500325000	Rice, flour	0.007
53234250	Cookie, peanut butter with rice cereal (no-bake)	1500325000	Rice, flour	26.7
53430100	Crepe, dessert type, chocolate-filled	1500325000	Rice, flour	0.003
53452150	Pastry, Chinese, made with rice flour	1500325000	Rice, flour	25.6
53521210	Doughnut, custard-filled	1500325000	Rice, flour	0.007
53530010	Breakfast tart, lowfat	1500325000	Rice, flour	0.17
53540200	Breakfast bar, cereal crust with fruit filling, lowfat	1500325000	Rice, flour	0.04
53540300	Fiber One Chewy Bar	1500324000	Rice, brown	17.39
53540400	Kellogg's Nutri-Grain Cereal Bar	1500325000	Rice, flour	0.04
53540402	Kellogg's Nutri-Grain Yogurt Bar	1500325000	Rice, flour	0.05
53540404	Kellogg's Nutri-Grain Fruit and Nut Bar	1500325000	Rice, flour	18.35
53540700	Kellogg's Special K bar	1500323000	Rice, white	42.3
53540800	Kashi GOLEAN Chewy Bars	1500324000	Rice, brown	4.38
53540800	Kashi GOLEAN Chewy Bars	1500325000	Rice, flour	0.56
53540802	Kashi TLC Chewy Granola Bar	1500324000	Rice, brown	6.55
53540802	Kashi TLC Chewy Granola Bar	1500325000	Rice, flour	0.56
53540804	Kashi GOLEAN Crunchy Bars	1500324000	Rice, brown	4.54
53540804	Kashi GOLEAN Crunchy Bars	1500325000	Rice, flour	0.58
53540806	Kashi TLC Crunchy Granola Bar	1500324000	Rice, brown	4.59
53540806	Kashi TLC Crunchy Granola Bar	1500325000	Rice, flour	0.59
53540900	Nature Valley Chewy Trail Mix Granola Bar	1500325000	Rice, flour	20.49
53540902	Nature Valley Chewy Granola Bar with Yogurt Coating	1500325000	Rice, flour	3.86
53540904	Nature Valley Sweet and Salty Nut Granola Bar	1500325000	Rice, flour	3.42
53541000	Quaker Chewy Granola Bar	1500325000	Rice, flour	24.08
53541002	Quaker Chewy 90 Calorie Granola Bar	1500324000	Rice, brown	6.55
53541002	Quaker Chewy 90 Calorie Granola Bar	1500325000	Rice, flour	0.56
53541004	Quaker Chewy 25% Less Sugar Granola Bar	1500323000	Rice, white	2.15
53541006	Quaker Chewy Dipps Granola Bar	1500325000	Rice, flour	3.77
53542000	Snack bar, oatmeal	1500325000	Rice, flour	19.11
53542200	Granola bar, lowfat, NFS	1500325000	Rice, flour	20.49
53542210	Granola bar, nonfat	1500324000	Rice, brown	42.64
53543000	Granola bar, reduced sugar, NFS	1500325000	Rice, flour	25.07
53543000	Granola bar, reduced sugar, NFS	1500325000	Rice, flour	27.38
53544200	Granola bar, chocolate-coated, NFS	1500325000	Rice, flour	3.77
53544210	Granola bar, with coconut, chocolate-coated	1500325000	Rice, flour	1.44
53544220	Granola bar with nuts, chocolate-coated	1500325000	Rice, flour	8.36
53544230	Granola bar, oats, nuts, coated with non-chocolate coating	1500325000	Rice, flour	3.42
53544250	Granola bar, coated with non-chocolate coating	1500325000	Rice, flour	3.74
53544300	Granola bar, high fiber, coated with non-chocolate yogurt coating	1500324000	Rice, brown	17.96
53544400	Granola bar, with rice cereal	1500325000	Rice, flour	24.08
53544410	Quaker Granola Bites	1500323000	Rice, white	2.15
53544450	PowerBar (fortified high energy bar)	1500324000	Rice, brown	7.54

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53544450	PowerBar (fortified high energy bar)	1500325000	Rice, flour	0.16
53801000	Cereal bar with fruit filling, baby food	1500325001	Rice, flour-babyfood	0.04
54102090	Crackers, graham, higher fat	1500325000	Rice, flour	0.009
54102200	Crackers, graham, sandwich-type, with filling	1500325000	Rice, flour	0.007
54206010	Puffed rice cake without salt	1500324000	Rice, brown	99.99
54304100	Cracker, cheese, reduced fat	1500325000	Rice, flour	0.05
54318500	Rice cake, cracker-type	1500324000	Rice, brown	98.17
54319000	Crackers, rice	1500323000	Rice, white	94.89
54319010	Puffed rice cake	1500324000	Rice, brown	99.55
54319020	Popcorn cake	1500324000	Rice, brown	14.37
54319500	Rice paper	1500325000	Rice, flour	85
54350010	Gerber Finger Foods, Puffs, baby food	1500325001	Rice, flour-babyfood	34.9
54401120	Salty snacks, corn or cornmeal base, tortilla chips, fat free, made with Olean	1500325000	Rice, flour	0.08
54402500	Salty snacks, wheat- and corn-based chips	1500325000	Rice, flour	1
54402600	Salty snacks, multigrain, chips	1500325000	Rice, flour	2.15
54406010	Snacks, onion-flavored rings	1500325000	Rice, flour	0.01
54408070	Pretzel, hard, multigrain	1500324000	Rice, brown	16.07
54420100	Oriental party mix, with peanuts, sesame sticks, chili rice crackers and fried green peas	1500324000	Rice, brown	22.95
55207000	Waffle, multi-bran	1500326000	Rice, bran	1.74
55501000	Flour and water patty	1500323000	Rice, white	56.75
55701000	Cake made with glutinous rice	1500323000	Rice, white	63.65
55702000	Cake or pancake made with rice flour and/or dried beans	1500325000	Rice, flour	53.13
55703000	Cake made with glutinous rice and dried beans	1500323000	Rice, white	31.25
56117090	Chow fun rice noodles, cooked, NS as to fat added in cooking	1500325000	Rice, flour	29.22
56117100	Chow fun rice noodles, cooked, fat not added in cooking	1500325000	Rice, flour	29.22
56117110	Chow fun rice noodles, cooked, fat added in cooking	1500325000	Rice, flour	28.39
56201240	Grits, cooked, flavored, corn or hominy, instant, fat not added in cooking	1500325000	Rice, flour	0.005
56201250	Grits, cooked, flavored, corn or hominy, instant, fat added in cooking	1500325000	Rice, flour	0.004
56201260	Grits, cooked, flavored, corn or hominy, instant, NS as to fat added in cooking	1500325000	Rice, flour	0.005
56204980	Rice, white, cooked, converted, NS as to fat added in cooking	1500323000	Rice, white	30.62
56204990	Rice, white, cooked, regular, NS as to fat added in cooking	1500323000	Rice, white	35.7
56205000	Rice, cooked, NFS	1500323000	Rice, white	35.7
56205010	Rice, white, cooked, regular, fat not added in cooking	1500323000	Rice, white	35.7
56205020	Rice, white, cooked, instant, NS as to fat added in cooking	1500323000	Rice, white	25.6
56205030	Rice, white, cooked, instant, fat not added in cooking	1500323000	Rice, white	25.6
56205040	Rice, white, cooked, converted, fat not added in cooking	1500323000	Rice, white	30.62
56205050	Rice, cream of, cooked, fat not added in cooking	1500323000	Rice, white	14
56205060	Rice, cooked, with milk	1500323000	Rice, white	25.4
56205070	Rice, sweet (rice, cooked, with honey)	1500323000	Rice, white	33.5
56205080	Rice, creamed, made with milk and sugar, Puerto Rican style	1500323000	Rice, white	10.79
56205090	Rice, cream of, cooked, fat added in cooking	1500323000	Rice, white	13.52
56205110	Rice, brown, cooked, regular, fat not added in cooking	1500324000	Rice, brown	30
56205120	Rice, brown, cooked, regular, NS as to fat added in cooking	1500324000	Rice, brown	30
56205130	Yellow rice, cooked, regular, NS as to fat added in cooking	1500323000	Rice, white	24.46
56205150	Yellow rice, cooked, regular, fat not added in cooking	1500323000	Rice, white	25.01

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56205170	Yellow rice, cooked, regular, fat added in cooking	1500323000	Rice, white	24.46
56205190	Rice, white, cooked, glutinous	1500323000	Rice, white	26.1
56205200	Rice, frozen dessert, nondairy, flavors other than chocolate	1500324000	Rice, brown	22.57
56205230	Rice dessert bar, frozen, flavors other than chocolate, nondairy, carob covered	1500324000	Rice, brown	20.4
56205300	Rice, white and wild, cooked, fat not added in cooking	1500323000	Rice, white	22.55
56205310	Rice, brown and wild, cooked, fat not added in cooking	1500324000	Rice, brown	22.55
56205320	Rice, white and wild, cooked, fat added in cooking	1500323000	Rice, white	22.1
56205330	Rice, white and wild, cooked, NS as to fat added in cooking	1500323000	Rice, white	22.1
56205340	Rice, brown and wild, cooked, fat added in cooking	1500324000	Rice, brown	22.1
56205350	Rice, brown and wild, cooked, NS as to fat added in cooking	1500324000	Rice, brown	22.1
56205400	Rice, cooked, NS as to type, fat added in cooking	1500323000	Rice, white	33.7
56205410	Rice, white, cooked with (fat) oil, Puerto Rican style (Arroz blanco)	1500323000	Rice, white	46.1
56205420	Rice, white, cooked, regular, fat added in cooking	1500323000	Rice, white	33.7
56205430	Rice, white, cooked, instant, fat added in cooking	1500323000	Rice, white	24.22
56205440	Rice, white, cooked, converted, fat added in cooking	1500323000	Rice, white	29.06
56205510	Rice, brown, cooked, regular, fat added in cooking	1500324000	Rice, brown	28.62
56205530	Rice, brown, cooked, instant, NS as to fat added in cooking	1500324000	Rice, brown	28.61
56205540	Rice, brown, cooked, instant, fat not added in cooking	1500324000	Rice, brown	30
56205550	Rice, brown, cooked, instant, fat added in cooking	1500324000	Rice, brown	28.61
57000000	Cereal, NFS	1500325000	Rice, flour	23.96
57000050	Kashi cereal, NS as to ready to eat or cooked	1500324000	Rice, brown	15.13
57000100	Oat cereal, NFS	1500324000	Rice, brown	0.21
57000100	Oat cereal, NFS	1500325000	Rice, flour	1.14
57100100	Cereal, ready-to-eat, NFS	1500325000	Rice, flour	9.59
57100400	Character cereals, TV or movie, General Mills	1500325000	Rice, flour	23.96
57100500	Character cereals, TV or movie, Kellogg's	1500325000	Rice, flour	23.96
57101500	Almond Delight	1500323000	Rice, white	18.4
57103400	Apple Cinnamon Oh's Cereal	1500325000	Rice, flour	3.46
57106050	Banana Nut Crunch Cereal (Post)	1500323000	Rice, white	5.78
57106100	Basic 4	1500324000	Rice, brown	9.79
57106100	Basic 4	1500325000	Rice, flour	9.25
57106530	Blueberry Morning, Post	1500323000	Rice, white	11.56
57120000	Cap'n Crunch's Peanut Butter Crunch	1500325000	Rice, flour	5.21
57123000	Cheerios	1500325000	Rice, flour	0.04
57124200	Chocolate flavored frosted puffed corn cereal	1500325000	Rice, flour	0.03
57125000	Cinnamon Toast Crunch	1500325000	Rice, flour	22.07
57125010	Cinnamon Toast Crunch Reduced Sugar	1500325000	Rice, flour	22.65
57126000	Cocoa Krispies	1500325000	Rice, flour	54.42
57127000	Cocoa Pebbles	1500323000	Rice, white	50.68
57130000	Cookie-Crisp	1500323000	Rice, white	18.09
57130000	Cookie-Crisp	1500325000	Rice, flour	0.02
57143500	Cranberry Almond Crunch, Post	1500323000	Rice, white	13.42
57148000	Crispix	1500323000	Rice, white	46.9
57148500	Crispy Brown Rice Cereal	1500324000	Rice, brown	106.04
57148600	Harmony cereal, General Mills	1500325000	Rice, flour	7.59
57151000	Crispy Rice	1500325000	Rice, flour	94.46
57160000	Curves Fruit and Nut Crunch Cereal	1500323000	Rice, white	19.15
57215000	Frosty O's	1500325000	Rice, flour	0.03

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57218000	Frosted Rice Krispies, Kellogg's	1500323000	Rice, white	66.65
57219000	Fruit & Fibre (fiber), NFS	1500323000	Rice, white	3.96
57221650	Fruit Harvest cereal, Kellogg's	1500323000	Rice, white	3.96
57223000	Fruity Pebbles	1500323000	Rice, white	54.47
57229000	Granola, lowfat, Kellogg's	1500323000	Rice, white	2.17
57229500	Granola with Raisins, lowfat, Kellogg's	1500323000	Rice, white	2.18
57232100	Healthy Choice Almond Crunch with raisins, Kellogg's	1500323000	Rice, white	1.22
57232100	Healthy Choice Almond Crunch with raisins, Kellogg's	1500324000	Rice, brown	2.19
57232120	Healthy Choice Multi-Grain Flakes, Kellogg's	1500324000	Rice, brown	4.24
57237100	Honey Bunches of Oats	1500323000	Rice, white	1.25
57237200	Honey Bunches of Oats with Vanilla Clusters, Post	1500323000	Rice, white	1.21
57237300	Honey Bunches of Oats with Almonds, Post	1500323000	Rice, white	1.23
57240100	Honey Nut Chex	1500323000	Rice, white	62.02
57244000	Just Right	1500323000	Rice, white	24.18
57245000	Just Right Fruit and Nut (formerly Just Right with raisins, dates, and nuts)	1500323000	Rice, white	19.44
57301500	Kashi, Puffed	1500324000	Rice, brown	15.13
57301510	Kashi GOLEAN	1500324000	Rice, brown	11.24
57301511	Kashi GOLEAN Crunch	1500324000	Rice, brown	10.88
57301512	Kashi GOLEAN Crunch Honey Almond Flax	1500324000	Rice, brown	10.26
57301520	Kashi Good Friends	1500324000	Rice, brown	8.55
57301520	Kashi Good Friends	1500325000	Rice, flour	2.21
57301530	Kashi Heart to Heart Honey Toasted Oat	1500324000	Rice, brown	8.29
57302100	King Vitaman	1500325000	Rice, flour	0.21
57305200	Malt-O-Meal Crispy Rice	1500325000	Rice, flour	95.83
57306100	Malt-O-Meal Puffed Rice	1500325000	Rice, flour	108.71
57306700	Malt-O-Meal Toasted Oat Cereal	1500325000	Rice, flour	0.04
57307010	Maple Pecan Crunch Cereal, Post	1500323000	Rice, white	5.55
57307100	Fruity Marshmallow Krispies (formerly called Marshmallow Krispies)	1500323000	Rice, white	56.13
57307100	Fruity Marshmallow Krispies (formerly called Marshmallow Krispies)	1500325000	Rice, flour	0.18
57308150	Mueslix cereal, NFS	1500323000	Rice, white	1.54
57308150	Mueslix cereal, NFS	1500324000	Rice, brown	4.81
57308190	Muesli, dried fruit and nuts (formerly Muesli with raisins, dates, and almonds)	1500323000	Rice, white	6.56
57308300	Multi Bran Chex	1500326000	Rice, bran	1.55
57308400	MultiGrain Cheerios	1500324000	Rice, brown	9.65
57316100	Nutri-Grain Almond Raisin	1500324000	Rice, brown	46.07
57316300	Oat Bran Flakes, Health Valley	1500324000	Rice, brown	4.33
57316410	Oatmeal Crisp, Apple Cinnamon (formerly Oatmeal Crisp with Apples)	1500323000	Rice, white	15.25
57316450	Oatmeal Crisp with Almonds	1500323000	Rice, white	25.05
57316500	Oatmeal Crisp, Raisin (formerly Oatmeal Raisin Crisp)	1500323000	Rice, white	31.22
57316710	Oh's, Honey Graham	1500323000	Rice, white	0.66
57316710	Oh's, Honey Graham	1500325000	Rice, flour	0.66
57319500	Sun Country 100% Natural Granola, with Almonds	1500323000	Rice, white	25.05
57321500	100 % Natural Wholegrain Cereal with raisins, lowfat, Quaker	1500325000	Rice, flour	1.91
57321700	Optimum, Nature's Path	1500325000	Rice, flour	7.96
57321800	Optimum Slim, Nature's Path	1500325000	Rice, flour	7.96
57324000	Peanut Butter Toast Crunch, General Mills	1500325000	Rice, flour	5.18

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57325000	Product 19	1500323000	Rice, white	3.16
57327500	Quaker Oatmeal Squares (formerly Quaker Oat Squares)	1500325000	Rice, flour	0.01
57330010	Raisin Bran Crunch, Kellogg's	1500323000	Rice, white	19.02
57336000	Rice Chex	1500325000	Rice, flour	98.08
57337000	Rice Flakes, NFS	1500325000	Rice, flour	94.46
57339000	Rice Krispies, Kellogg's	1500325000	Rice, flour	95.83
57339100	Rice Krispies with Real Strawberries, Kellogg's	1500325000	Rice, flour	83.82
57339500	Rice Krispies Treats Cereal, Kellogg's	1500323000	Rice, white	56.13
57339500	Rice Krispies Treats Cereal, Kellogg's	1500325000	Rice, flour	0.18
57340000	Rice, puffed	1500325000	Rice, flour	108.71
57341200	Smart Start Strong Heart Antioxidants Cereal, Kellogg's	1500324000	Rice, brown	4.24
57344000	Special K	1500323000	Rice, white	77.31
57344005	Special K Chocolatey Delight	1500323000	Rice, white	71.65
57344010	Special K Red Berries	1500323000	Rice, white	65.31
57344015	Special K Fruit & Yogurt	1500323000	Rice, white	48.81
57344015	Special K Fruit & Yogurt	1500323000	Rice, white	67.22
57344020	Special K Vanilla Almond	1500323000	Rice, white	63.03
57344025	Special K Cinnamon Pecan, Kellogg's	1500323000	Rice, white	59.34
57346500	Oatmeal Honey Nut Heaven, Quaker (formerly Toasted Oatmeal, Honey Nut)	1500325000	Rice, flour	0.97
57401100	Toasted oat cereal	1500325000	Rice, flour	22.27
57419000	Yogurt Burst Cheerios	1500325000	Rice, flour	0.04
57603100	Rice polishings	1500326000	Rice, bran	100
57803000	Mixed cereal, baby food, dry, instant	1500325001	Rice, flour-babyfood	20
57805000	Rice cereal, baby food, dry, instant	1500325001	Rice, flour-babyfood	100
57805080	Rice cereal with apples, baby food, dry, instant	1500325001	Rice, flour-babyfood	87.3
57805100	Rice cereal with bananas, baby food, dry, instant	1500325001	Rice, flour-babyfood	45
57805500	Brown rice cereal, baby food, dry, instant	1500324001	Rice, brown-babyfood	100
57806000	Mixed cereal with bananas, baby food, dry, instant	1500325001	Rice, flour-babyfood	17
57820000	Cereal, baby food, jarred, NFS	1500325001	Rice, flour-babyfood	4.2
57820100	Rice cereal, baby food, jarred, NFS	1500325001	Rice, flour-babyfood	8
57822000	Mixed cereal with applesauce and bananas, baby food, jarred	1500325001	Rice, flour-babyfood	6.5
57824000	Rice cereal with applesauce and bananas, baby food, jarred	1500325001	Rice, flour-babyfood	8
57824500	Rice cereal with mixed fruit, baby food, jarred	1500325001	Rice, flour-babyfood	15
57830100	Gerber Graduates Finger Snacks Cereal, baby food	1500325001	Rice, flour-babyfood	15
58100155	Burrito with beef, rice, and cheese	1500323000	Rice, white	8.03
58100160	Burrito with beef, beans, rice, and cheese	1500323000	Rice, white	5.74
58100250	Burrito with chicken, rice, and cheese	1500323000	Rice, white	28.44
58100255	Burrito with chicken, beans, rice, and cheese	1500323000	Rice, white	13.45
58100300	Burrito with beans and rice, meatless	1500323000	Rice, white	8.48
58100330	Burrito with rice, beans, cheese, sour cream, lettuce, tomato and guacamole, meatless	1500323000	Rice, white	1.11
58104160	Nachos with chili	1500325000	Rice, flour	0.02
58104180	Nachos with beef, beans, cheese, tomatoes, sour cream and onions	1500325000	Rice, flour	0.08
58104600	Chimichanga with beef and rice	1500323000	Rice, white	6.57
58106347	Pizza with cheese and extra vegetables, regular crust	1500325000	Rice, flour	0.001
58106412	Pizza with chicken, regular crust	1500325000	Rice, flour	0.001
58106443	Pizza with chicken and vegetables, thick crust	1500325000	Rice, flour	0.001

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58106462	Pizza with chicken and fruit, regular crust	1500325000	Rice, flour	0.001
58106500	Pizza with meat, prepared from frozen, thin crust	1500325000	Rice, flour	0.001
58106505	Pizza with meat, prepared from frozen, thick crust	1500325000	Rice, flour	0.001
58106510	Pizza with meat, NS as to type of crust	1500325000	Rice, flour	0.001
58106520	Pizza with meat, thin crust	1500325000	Rice, flour	0.001
58106530	Pizza with meat, thick crust	1500325000	Rice, flour	0.001
58106540	Pizza with pepperoni, NS as to type of crust	1500325000	Rice, flour	0.001
58106550	Pizza with pepperoni, thin crust	1500325000	Rice, flour	0.001
58106555	Pizza with pepperoni, regular crust	1500325000	Rice, flour	0.001
58106560	Pizza with pepperoni, thick crust	1500325000	Rice, flour	0.001
58106610	Pizza with meat other than pepperoni, NS as to type of crust	1500325000	Rice, flour	0.001
58106620	Pizza with meat other than pepperoni, thin crust	1500325000	Rice, flour	0.001
58106625	Pizza with meat other than pepperoni, regular crust	1500325000	Rice, flour	0.001
58106630	Pizza with meat other than pepperoni, thick crust	1500325000	Rice, flour	0.001
58106640	Pizza with extra meat, NS as to type of crust	1500325000	Rice, flour	0.001
58106650	Pizza with extra meat, thin crust	1500325000	Rice, flour	0.001
58106655	Pizza with extra meat, regular crust	1500325000	Rice, flour	0.001
58106660	Pizza with extra meat, thick crust	1500325000	Rice, flour	0.001
58106700	Pizza with meat and vegetables, prepared from frozen, thin crust	1500325000	Rice, flour	0.001
58106705	Pizza with meat and vegetables, prepared from frozen, thick crust	1500325000	Rice, flour	0.001
58106710	Pizza with meat and vegetables, NS as to type of crust	1500325000	Rice, flour	0.001
58106720	Pizza with meat and vegetables, thin crust	1500325000	Rice, flour	0.001
58106725	Pizza with meat and vegetables, regular crust	1500325000	Rice, flour	0.001
58106730	Pizza with meat and vegetables, thick crust	1500325000	Rice, flour	0.001
58106733	Pizza with extra meat and extra vegetables, prepared from frozen, thin crust	1500325000	Rice, flour	0.001
58106734	Pizza with extra meat and extra vegetables, prepared from frozen, thick crust	1500325000	Rice, flour	0.001
58106735	Pizza with extra meat and extra vegetables, NS as to type of crust	1500325000	Rice, flour	0.001
58106736	Pizza with extra meat and extra vegetables, thin crust	1500325000	Rice, flour	0.001
58106737	Pizza with extra meat and extra vegetables, thick crust	1500325000	Rice, flour	0.001
58106738	Pizza with extra meat and extra vegetables, regular crust	1500325000	Rice, flour	0.001
58106740	Pizza with meat and fruit, NS as to type of crust	1500325000	Rice, flour	0.001
58106750	Pizza with meat and fruit, thin crust	1500325000	Rice, flour	0.001
58106755	Pizza with meat and fruit, regular crust	1500325000	Rice, flour	0.001
58106760	Pizza with meat and fruit, thick crust	1500325000	Rice, flour	0.001
58106780	Pizza with meat and vegetables, prepared from frozen, lowfat, thin crust	1500325000	Rice, flour	0.001
58108010	Calzone, with meat and cheese	1500325000	Rice, flour	0.001
58109010	Italian pie with meat	1500325000	Rice, flour	0.001
58110200	Roll with meat and/or shrimp, vegetables and rice paper (not fried)	1500325000	Rice, flour	10.85
58112110	Dim sum, meat filled (egg roll-type)	1500325000	Rice, flour	0.001
58116110	Meat turnover, Puerto Rican style (Pastelillo de carne; Empanadilla)	1500325000	Rice, flour	0.001
58116120	Empanada, Mexican turnover, filled with meat and vegetables	1500325000	Rice, flour	0.001
58121510	Dumpling, meat-filled	1500325000	Rice, flour	0.001
58123110	Sweet bread dough, filled with meat, steamed	1500325000	Rice, flour	0.01
58125110	Quiche with meat, poultry or fish	1500325000	Rice, flour	0.001
58126150	Turnover, meat- and cheese-filled, tomato-based sauce	1500325000	Rice, flour	0.001
58126270	Turnover, chicken- or turkey-, and cheese-filled, no gravy	1500325000	Rice, flour	0.001

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58126280	Turnover, chicken- or turkey-, and vegetable-filled, lower in fat	1500325000	Rice, flour	0.01
58126400	Turnover, filled with egg, meat and cheese	1500325000	Rice, flour	0.001
58127110	Vegetables in pastry	1500325000	Rice, flour	0.01
58127150	Vegetables and cheese in pastry	1500325000	Rice, flour	0.01
58127210	Croissant sandwich, filled with ham and cheese	1500325000	Rice, flour	0.001
58127290	Croissant sandwich with bacon and egg	1500325000	Rice, flour	0.001
58127350	Croissant sandwich with bacon, egg, and cheese	1500325000	Rice, flour	0.001
58128000	Biscuit with gravy	1500325000	Rice, flour	0.003
58128250	Dressing with meat and vegetables	1500325000	Rice, flour	0.001
58130013	Lasagna with meat, canned	1500325000	Rice, flour	0.03
58131323	Ravioli, meat-filled, with tomato sauce or meat sauce, canned	1500325000	Rice, flour	0.02
58131523	Ravioli, cheese-filled, with tomato sauce, canned	1500323000	Rice, white	0.38
58131523	Ravioli, cheese-filled, with tomato sauce, canned	1500325000	Rice, flour	0.01
58132110	Spaghetti with tomato sauce, meatless	1500325000	Rice, flour	0.01
58132310	Spaghetti with tomato sauce and meatballs or spaghetti with meat sauce or spaghetti with meat sauce and meatballs	1500325000	Rice, flour	0.009
58132313	Pasta with tomato sauce and meat or meatballs, canned	1500325000	Rice, flour	0.002
58132340	Spaghetti with tomato sauce and vegetables	1500325000	Rice, flour	0.01
58132350	Spaghetti with tomato sauce, meatless, whole wheat noodles	1500325000	Rice, flour	0.01
58132360	Spaghetti with tomato sauce and meatballs, whole wheat noodles or spaghetti with meat sauce, whole wheat noodles or spaghetti with meat sauce and meatballs, whole wheat noodles	1500325000	Rice, flour	0.009
58132450	Spaghetti with tomato sauce, meatless, made with spinach noodles	1500325000	Rice, flour	0.01
58132460	Spaghetti with tomato sauce and meatballs made with spinach noodles, or spaghetti with meat sauce made with spinach noodles, or spaghetti with meat sauce and meatballs made with spinach noodles	1500325000	Rice, flour	0.02
58132710	Spaghetti with tomato sauce and frankfurters or hot dogs	1500325000	Rice, flour	0.01
58132910	Spaghetti with tomato sauce and poultry	1500325000	Rice, flour	0.01
58134610	Tortellini, meat-filled, with tomato sauce	1500325000	Rice, flour	0.001
58134613	Tortellini, meat-filled, with tomato sauce, canned	1500325000	Rice, flour	0.009
58134650	Tortellini, meat-filled, no sauce	1500325000	Rice, flour	0.001
58135110	Chow fun noodles with meat and vegetables	1500325000	Rice, flour	15.91
58135120	Chow fun noodles with vegetables, meatless	1500325000	Rice, flour	24.78
58145150	Macaroni or noodles with cheese and pork or ham	1500325000	Rice, flour	0.001
58146130	Pasta with carbonara sauce	1500325000	Rice, flour	0.001
58146200	Pasta, meat-filled, with gravy, canned	1500325000	Rice, flour	0.004
58146300	Pasta, whole wheat, with meat sauce	1500325000	Rice, flour	0.02
58147340	Macaroni, creamed, with cheese and tuna	1500325000	Rice, flour	0.01
58148110	Macaroni or pasta salad	1500325000	Rice, flour	0.003
58148120	Macaroni or pasta salad with egg	1500325000	Rice, flour	0.003
58148130	Macaroni or pasta salad with tuna	1500325000	Rice, flour	0.003
58148140	Macaroni or pasta salad with crab meat	1500325000	Rice, flour	0.003
58148150	Macaroni or pasta salad with shrimp	1500325000	Rice, flour	0.003
58148160	Macaroni or pasta salad with tuna and egg	1500325000	Rice, flour	0.003
58150110	Rice, fried, meatless	1500323000	Rice, white	23.94
58150310	Rice, fried, NFS	1500323000	Rice, white	24.24
58150320	Rice, fried, with chicken	1500323000	Rice, white	24.24
58150330	Rice, fried, with pork	1500323000	Rice, white	24.24

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58150340	Rice, fried, with beef	1500323000	Rice, white	24.31
58150510	Rice, fried, with shrimp	1500323000	Rice, white	24.38
58151100	Sushi, NFS	1500323000	Rice, white	27.87
58151110	Sushi, no vegetables, no seafood (no fish or shellfish)	1500323000	Rice, white	43.9
58151120	Sushi, with vegetables, no seafood (no fish or shellfish)	1500323000	Rice, white	29.34
58151130	Sushi, with vegetables and seafood	1500323000	Rice, white	25.85
58151140	Sushi, with vegetables, rolled in seaweed	1500323000	Rice, white	26.3
58151150	Sushi, with seafood, no vegetables	1500323000	Rice, white	29.04
58155110	Rice with chicken, Puerto Rican style (Arroz con Pollo)	1500323000	Rice, white	38.32
58155110	Rice with chicken, Puerto Rican style (Arroz con Pollo)	1500325000	Rice, flour	0.001
58155310	Paella, Valenciana style, with meat (Paella Valenciana)	1500323000	Rice, white	16.72
58155320	Seafood paella, Puerto Rican style	1500323000	Rice, white	7.76
58155410	Soupy rice with chicken, Puerto Rican style (Asopao de pollo)	1500323000	Rice, white	13.39
58155410	Soupy rice with chicken, Puerto Rican style (Asopao de pollo)	1500325000	Rice, flour	0.001
58155510	Soupy rice mixture with chicken and potatoes, Puerto Rican style	1500323000	Rice, white	8.64
58155510	Soupy rice mixture with chicken and potatoes, Puerto Rican style	1500325000	Rice, flour	0.001
58155610	Rice meal fritter, Puerto Rican style (Almojabana)	1500325000	Rice, flour	22.86
58155810	Stewed rice, Puerto Rican style (arroz guisado)	1500323000	Rice, white	39.61
58155810	Stewed rice, Puerto Rican style (arroz guisado)	1500325000	Rice, flour	0.001
58156210	Rice with vienna sausage, Puerto Rican style (arroz con salchichas)	1500323000	Rice, white	40.63
58156210	Rice with vienna sausage, Puerto Rican style (arroz con salchichas)	1500325000	Rice, flour	0.001
58156310	Rice with Spanish sausage, Puerto Rican style	1500323000	Rice, white	39.17
58156310	Rice with Spanish sausage, Puerto Rican style	1500325000	Rice, flour	0.001
58156410	Rice with onions, Puerto Rican style (arroz con cebollas)	1500323000	Rice, white	16.17
58156410	Rice with onions, Puerto Rican style (arroz con cebollas)	1500325000	Rice, flour	0.005
58156610	Pigeon pea asopao (Asopao de gandules)	1500323000	Rice, white	23.02
58156610	Pigeon pea asopao (Asopao de gandules)	1500325000	Rice, flour	0.001
58156710	Rice with stewed beans, Puerto Rican style	1500323000	Rice, white	25.78
58157210	Rice pudding made with coconut milk, Puerto Rican style	1500323000	Rice, white	9.23
58160110	Rice with beans	1500323000	Rice, white	15.85
58160120	Rice with beans and tomatoes	1500323000	Rice, white	11.85
58160130	Rice with beans and chicken	1500323000	Rice, white	11.36
58160135	Rice with beans and beef	1500323000	Rice, white	13.53
58160140	Rice with beans and pork	1500323000	Rice, white	11.89
58160150	Red beans and rice	1500323000	Rice, white	11.95
58160160	Hopping John (blackeye peas and rice)	1500323000	Rice, white	10.47
58160200	Rice with vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce, NS as to fat added in cooking	1500323000	Rice, white	27.42
58160202	Rice with vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce, fat not added in cooking	1500323000	Rice, white	24.54
58160204	Rice with vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce, fat added in cooking	1500323000	Rice, white	10.72
58160205	Rice with vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce, NS as to fat added in cooking	1500323000	Rice, white	23.89
58160207	Rice with vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce, fat not added in cooking	1500323000	Rice, white	24.54
58160209	Rice with vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce, fat added in cooking	1500323000	Rice, white	23.89
58160210	Rice with vegetables, no sauce	1500323000	Rice, white	17.49

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58160220	Rice with vegetables, tomato-based sauce (mixture)	1500323000	Rice, white	11.63
58160290	Rice with corn, NS as to fat added in cooking	1500323000	Rice, white	26.03
58160292	Rice with corn, fat not added in cooking	1500323000	Rice, white	26.43
58160294	Rice with corn, fat added in cooking	1500323000	Rice, white	24.98
58160300	Rice with peas, NS as to fat added in cooking	1500323000	Rice, white	27.36
58160302	Rice with peas, fat not added in cooking	1500323000	Rice, white	26.85
58160304	Rice with peas, fat added in cooking	1500323000	Rice, white	26.08
58160310	Rice with peas and carrots, NS as to fat added in cooking	1500323000	Rice, white	26.08
58160312	Rice with peas and carrots, fat not added in cooking	1500323000	Rice, white	28.37
58160314	Rice with peas and carrots, fat added in cooking	1500323000	Rice, white	26.08
58160320	Rice with tomatoes, NS as to fat added in cooking	1500323000	Rice, white	26.43
58160322	Rice with tomatoes, fat not added in cooking	1500323000	Rice, white	26.43
58160324	Rice with tomatoes, fat added in cooking	1500323000	Rice, white	25.44
58161110	Rice casserole with cheese	1500323000	Rice, white	23
58161120	Brown rice casserole with cheese	1500324000	Rice, brown	5.41
58161200	Rice, cooked with coconut milk (Arroz con coco)	1500323000	Rice, white	23.35
58161300	White rice with tomato sauce	1500323000	Rice, white	23.23
58161310	Rice, brown, with tomato sauce	1500324000	Rice, brown	20.9
58161320	Rice, brown, with beans	1500324000	Rice, brown	15.85
58161325	Rice, brown, with beans and tomatoes	1500324000	Rice, brown	11.48
58161400	Rice, brown, with vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce, NS as to fat added in cooking	1500324000	Rice, brown	17.49
58161402	Rice, brown, with vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce, fat not added in cooking	1500324000	Rice, brown	56.92
58161404	Rice, brown, with vegetables (including carrots, broccoli, and/or dark-green leafy), no sauce, fat added in cooking	1500324000	Rice, brown	54.59
58161405	Rice, brown, with vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce, NS as to fat added in cooking	1500324000	Rice, brown	21.44
58161407	Rice, brown, with vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce, fat not added in cooking	1500324000	Rice, brown	21.93
58161409	Rice, brown, with vegetables (excluding carrots, broccoli, and dark-green leafy), no sauce, fat added in cooking	1500324000	Rice, brown	66.4
58161422	Rice, brown, with corn, fat not added in cooking	1500324000	Rice, brown	23.56
58161430	Rice, brown, with peas, NS as to fat added in cooking	1500324000	Rice, brown	23.1
58161432	Rice, brown, with peas, fat not added in cooking	1500324000	Rice, brown	65.81
58161452	Rice, brown, with tomatoes, fat not added in cooking	1500324000	Rice, brown	26.43
58161454	Rice, brown, with tomatoes, fat added in cooking	1500324000	Rice, brown	15.68
58161510	Grape leaves stuffed with rice	1500323000	Rice, white	8.41
58161710	Rice croquette	1500323000	Rice, white	19.99
58162110	Stuffed pepper, with rice and meat	1500323000	Rice, white	6.76
58162120	Stuffed pepper, with rice, meatless	1500323000	Rice, white	10.21
58162140	Stuffed tomato, with rice, meatless	1500323000	Rice, white	11.6
58162310	Rice pilaf	1500323000	Rice, white	25.49
58163110	Rice with gravy	1500323000	Rice, white	26.09
58163130	Dirty rice	1500323000	Rice, white	22.03
58163210	Rice, creamed	1500323000	Rice, white	25.58
58163310	Flavored rice mixture	1500323000	Rice, white	22.67
58163330	Flavored rice mixture with cheese	1500323000	Rice, white	15.16
58163330	Flavored rice mixture with cheese	1500325000	Rice, flour	0.001

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58163350	Flavored rice, white and wild	1500323000	Rice, white	17.65
58163360	Flavored rice, brown and wild	1500324000	Rice, brown	16.1
58163360	Flavored rice, brown and wild	1500325000	Rice, flour	0.001
58163380	Flavored rice and pasta mixture	1500323000	Rice, white	10.58
58163400	Flavored rice and pasta mixture, reduced sodium	1500323000	Rice, white	10.61
58163410	Spanish rice	1500323000	Rice, white	15.45
58163450	Spanish rice with ground beef	1500323000	Rice, white	8.03
58163510	Rice dressing	1500323000	Rice, white	17.86
58163610	Rice-vegetable medley	1500323000	Rice, white	23.05
58164110	Rice with raisins	1500323000	Rice, white	32.03
58164210	Rice dessert or salad with fruit	1500323000	Rice, white	11.71
58200100	Wrap sandwich, filled with meat, poultry, or fish, vegetables, and rice	1500323000	Rice, white	9.55
58200300	Wrap sandwich, filled with meat, poultry, or fish, vegetables, rice, and cheese	1500323000	Rice, white	9.61
58301020	Lasagna with cheese and sauce (diet frozen meal)	1500325000	Rice, flour	0.02
58302060	Spaghetti or noodles with beef in tomato-based sauce, lowfat, reduced sodium (diet frozen meal)	1500325000	Rice, flour	0.001
58302080	Noodles with vegetables in tomato-based sauce (diet frozen meal)	1500325000	Rice, flour	0.001
58303100	Rice, with broccoli, cheese sauce (frozen side dish)	1500323000	Rice, white	19.39
58303200	Rice, with green beans, water chestnuts, in sherry mushroom sauce (frozen side dish)	1500323000	Rice, white	10.71
58304230	Ravioli, cheese-filled, with vegetable and fruit (frozen meal)	1500325000	Rice, flour	0.02
58305100	Macaroni or noodles, spinach, with chicken and cheese sauce (diet frozen meal)	1500325000	Rice, flour	0.008
58305200	Pasta, spinach, with vegetables and cheese sauce (diet frozen meal)	1500325000	Rice, flour	0.006
58305250	Pasta with vegetable and cheese sauce (diet frozen meal)	1500325000	Rice, flour	0.004
58306010	Beef enchilada dinner, NFS (frozen meal)	1500323000	Rice, white	6.91
58306020	Beef enchilada, chili gravy, rice, refried beans (frozen meal)	1500323000	Rice, white	6.91
58306050	Cheese enchilada with beans and rice (frozen meal)	1500323000	Rice, white	7.28
58306150	Chicken enchilada with salsa, rice, vegetable, and dessert (diet frozen meal)	1500323000	Rice, white	6.65
58306200	Chicken fajitas (diet frozen meal)	1500325000	Rice, flour	0.001
58310210	Sausage and french toast (frozen meal)	1500325000	Rice, flour	0.00028
58310310	Pancakes and sausage (frozen meal)	1500325000	Rice, flour	0.001
58400200	Rice soup, NFS	1500323000	Rice, white	3.22
58402030	Beef rice soup	1500323000	Rice, white	5.2
58404010	Chicken or turkey rice soup, canned, or ready-to-serve	1500323000	Rice, white	2.86
58404030	Chicken or turkey rice soup, home recipe	1500323000	Rice, white	3.96
58404040	Chicken rice soup, canned, reduced sodium, prepared with water or ready-to-serve	1500323000	Rice, white	2.49
58404050	Chicken rice soup, canned, reduced sodium, prepared with milk	1500323000	Rice, white	2.49
58404100	Rice and potato soup, Puerto Rican style	1500323000	Rice, white	12.48
58404100	Rice and potato soup, Puerto Rican style	1500325000	Rice, flour	0.001
58407000	Instant soup, NFS	1500325000	Rice, flour	0.001
58407010	Instant soup, noodle	1500325000	Rice, flour	0.001
58407040	Instant soup, rice	1500323000	Rice, white	3.22
58421000	Sopa seca (dry soup), Mexican style, NFS	1500323000	Rice, white	11.79
58421060	Sopa seca de arroz (dry rice soup), Mexican style	1500323000	Rice, white	22.81
58503000	Macaroni, tomatoes, and beef, baby food, NS as to strained or junior	1500325001	Rice, flour-babyfood	2

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58503010	Macaroni, tomatoes, and beef, baby food, strained	1500325001	Rice, flour-babyfood	4
58508000	Macaroni and cheese, baby food, strained	1500325001	Rice, flour-babyfood	2
58508300	Macaroni and cheese, baby food, toddler	1500325001	Rice, flour-babyfood	0.01
63401010	Apple salad with dressing	1500325000	Rice, flour	0.003
63412010	Pear salad with dressing	1500325000	Rice, flour	0.003
63413010	Pineapple salad with dressing	1500325000	Rice, flour	0.0017
63420200	Fruit juice bar, frozen, sweetened with low calorie sweetener, flavors other than orange	1500325000	Rice, flour	0.005
67304030	Plums, bananas, and rice, baby food strained	1500324001	Rice, brown-babyfood	5
67408010	Banana pudding, baby food, strained	1500325001	Rice, flour-babyfood	10
67414010	Pineapple dessert, baby food, strained	1500325001	Rice, flour-babyfood	10
67415010	Tutti-fruitti pudding, baby food, strained	1500325001	Rice, flour-babyfood	0.09
67415020	Tutti-fruitti pudding, baby food, junior	1500325001	Rice, flour-babyfood	0.06
71201090	White potato, chips, fat free, made with Olean	1500325000	Rice, flour	0.18
71201210	White potato, chips, restructured, fat free, made with Olean	1500325000	Rice, flour	0.12
71204000	Potato puffs, cheese-filled	1500325000	Rice, flour	0.24
71402505	White potato, french fries, with cheese and bacon	1500325000	Rice, flour	0.001
71411000	White potato skins, with adhering flesh, fried, with cheese and bacon	1500325000	Rice, flour	0.001
71501200	White potato, from complete dry mix, mashed, made with water	1500325000	Rice, flour	0.001
71507030	White potato, stuffed, baked, peel not eaten, stuffed with chili	1500325000	Rice, flour	0.008
71508030	White potato, stuffed, baked, peel eaten, stuffed with chili	1500325000	Rice, flour	0.006
71508060	White potato, stuffed, baked, peel eaten, stuffed with bacon and cheese	1500325000	Rice, flour	0.001
71508070	White potato, stuffed, baked, peel not eaten, stuffed with bacon and cheese	1500325000	Rice, flour	0.001
71508120	White potato, stuffed with ham, broccoli and cheese sauce, baked, peel eaten	1500325000	Rice, flour	0.001
71602010	Potato salad, German style	1500325000	Rice, flour	0.001
71801040	Potato soup, instant, made from dry mix	1500325000	Rice, flour	0.001
72201240	Broccoli, cooked, NS as to form, with mushroom sauce	1500325000	Rice, flour	0.03
72201241	Broccoli, cooked, from fresh, with mushroom sauce	1500325000	Rice, flour	0.03
72201242	Broccoli, cooked, from frozen, with mushroom sauce	1500325000	Rice, flour	0.03
72202020	Broccoli casserole (broccoli, rice, cheese, and mushroom sauce)	1500323000	Rice, white	10.57
72302100	Broccoli cheese soup, prepared with milk	1500325000	Rice, flour	0.01
73406010	Sweetpotato with fruit	1500325000	Rice, flour	0.01
73501010	Carrot with rice soup, cream of, prepared with milk	1500323000	Rice, white	3.71
74404010	Spaghetti sauce, meatless	1500325000	Rice, flour	0.02
74404020	Spaghetti sauce with vegetables, homemade-style	1500325000	Rice, flour	0.02
74404030	Spaghetti sauce with meat, canned, no extra meat added	1500325000	Rice, flour	0.02
74404060	Spaghetti sauce, meatless, fat free	1500325000	Rice, flour	0.02
74406050	Barbecue sauce, low sodium	1500325000	Rice, flour	0.01
74410110	Puerto Rican seasoning with ham	1500325000	Rice, flour	0.001
74602050	Tomato soup, instant type, prepared with water	1500325000	Rice, flour	1.67
74603010	Tomato beef soup, prepared with water	1500325000	Rice, flour	0.01
74604010	Tomato beef noodle soup, prepared with water	1500325000	Rice, flour	0.01
74604100	Tomato beef rice soup, prepared with water	1500323000	Rice, white	1.04
74605010	Tomato rice soup, prepared with water	1500323000	Rice, white	1.04
75141200	Cabbage salad or coleslaw with pineapple, with dressing	1500325000	Rice, flour	0.004
75144100	Lettuce, wilted, with bacon dressing	1500325000	Rice, flour	0.001

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
75145000	Seven-layer salad (lettuce salad made with a combination of onion, celery, green pepper, peas, mayonnaise, cheese, eggs, and/or bacon)	1500325000	Rice, flour	0.005
75414020	Mushrooms, stuffed	1500325000	Rice, flour	0.001
75418030	Squash, summer, casserole, with rice and tomato sauce	1500323000	Rice, white	7.39
75439500	Chow mein or chop suey, meatless, no noodles	1500323000	Rice, white	18.96
75440100	Vegetable combination (including carrots, broccoli, and/or dark-green leafy), cooked, with soy-based sauce	1500325000	Rice, flour	0.005
75440110	Vegetable combination (excluding carrots, broccoli, and dark-green leafy), cooked, with soy-based sauce	1500325000	Rice, flour	0.004
75440170	Vegetable sticks, breaded (including corn, carrots, and green beans)	1500325000	Rice, flour	5.09
75450600	Vegetable combination (including carrots, broccoli, and/or dark-green leafy), cooked, with butter sauce	1500325000	Rice, flour	0.007
75605010	Leek soup, cream of, prepared with milk	1500325000	Rice, flour	0.007
75607040	Mushroom soup, with meat broth, prepared with water	1500325000	Rice, flour	0.01
75607080	Mushroom with chicken soup, cream of, prepared with milk	1500325000	Rice, flour	0.03
75607090	Mushroom soup, cream of, canned, reduced sodium, NS as to made with milk or water	1500325000	Rice, flour	0.02
75607100	Mushroom soup, cream of, canned, reduced sodium, prepared with milk	1500325000	Rice, flour	0.02
75607140	Mushroom soup, cream of, canned, reduced sodium, prepared with water	1500325000	Rice, flour	0.02
75607150	Mushroom soup, cream of, canned, reduced sodium, undiluted	1500325000	Rice, flour	0.04
75608100	Onion soup, French	1500325000	Rice, flour	0.005
75609050	Pea soup, canned, low sodium, prepared with water	1500325000	Rice, flour	0.01
75649100	Vegetable soup, cream of, made from dry mix, low sodium, prepared with water	1500325000	Rice, flour	0.04
75651010	Vegetable bean soup, prepared with water or ready-to-serve	1500325000	Rice, flour	0.001
75651070	Vegetable rice soup, prepared with water	1500323000	Rice, white	5.04
75651080	Vegetable beef soup with rice, prepared with water or ready-to-serve	1500323000	Rice, white	2.67
75651110	Vegetable chicken rice soup, canned, prepared with water or ready-to-serve	1500323000	Rice, white	1.4
75652050	Vegetable beef soup with rice, home recipe	1500323000	Rice, white	2.38
76102010	Spinach, creamed, baby food, strained	1500325001	Rice, flour-babyfood	2
76102030	Broccoli, carrots and cheese, baby food, junior	1500325001	Rice, flour-babyfood	4.64
76205060	Corn and sweetpotatoes, baby food, strained	1500325001	Rice, flour-babyfood	2.82
76402000	Green beans and potatoes, baby food, strained	1500324001	Rice, brown-babyfood	5
76405000	Corn, creamed, baby food, NS as to strained or junior	1500325001	Rice, flour-babyfood	3.2
76405010	Corn, creamed, baby food, strained	1500325001	Rice, flour-babyfood	3.2
76405020	Corn, creamed, baby food, junior	1500325001	Rice, flour-babyfood	3.2
76501000	Vegetables and rice, baby food, strained	1500324001	Rice, brown-babyfood	5
76502000	Peas and brown rice, baby food	1500324001	Rice, brown-babyfood	15
76601010	Vegetable and bacon, baby food, strained	1500325001	Rice, flour-babyfood	2
76603010	Vegetable and beef, baby food, strained	1500325001	Rice, flour-babyfood	2
76603020	Vegetable and beef, baby food, junior	1500325001	Rice, flour-babyfood	2
76607010	Vegetable and ham, baby food, strained	1500323001	Rice, white-babyfood	2

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
76607020	Vegetable and ham, baby food, junior	1500323001	Rice, white-babyfood	3
76607030	Potatoes with cheese and ham, baby food, toddler	1500325001	Rice, flour-babyfood	0.01
76607100	Potatoes with cheese and broccoli, baby food, toddler	1500325001	Rice, flour-babyfood	0.09
76611010	Vegetable and turkey, baby food, strained	1500323001	Rice, white-babyfood	4.25
77121010	Fried stuffed potatoes, Puerto Rican style (Rellenos de papas)	1500325000	Rice, flour	0.12
77250110	Stuffed tannier fritters, Puerto Rican style (Alcapurrias)	1500325000	Rice, flour	0.001
77316010	Stuffed cabbage, with meat, Puerto Rican style (Repollo relleno con carne)	1500325000	Rice, flour	0
77316510	Stuffed cabbage, with meat and rice, Syrian dish, Puerto Rican style (Repollo relleno con carne y con arroz; Arabe Mihsy Melful)	1500323000	Rice, white	8.17
77563010	Puerto Rican stew (Salcocho / Sancocho)	1500325000	Rice, flour	0.001
81103041	Margarine-like spread, made with yogurt, stick, salted	1500325000	Rice, flour	0.2
81104010	Margarine-like spread, reduced calorie, about 40% fat, tub, salted	1500325000	Rice, flour	0.2
81104011	Margarine-like spread, reduced calorie, about 40% fat, made with yogurt, tub, salted	1500325000	Rice, flour	0.2
81104020	Margarine-like spread, reduced calorie, about 40% fat, stick, salted	1500325000	Rice, flour	0.001
81104050	Margarine-like spread, reduced calorie, about 20% fat, tub, salted	1500325000	Rice, flour	0.001
81104070	Margarine-like spread, reduced calorie, about 20% fat, tub, unsalted	1500325000	Rice, flour	0.001
81104100	Margarine-like spread, fat free, tub, salted	1500325000	Rice, flour	0.7
81104110	Margarine-like spread, fat free, liquid, salted	1500325000	Rice, flour	1.25
81106010	Butter replacement, fat-free powder	1500325000	Rice, flour	0.58
81201000	Animal fat or drippings	1500325000	Rice, flour	0.001
81302050	Tartar sauce	1500325000	Rice, flour	0.01
81312000	Tartar sauce, low calorie	1500325000	Rice, flour	0.09
83101500	Bacon dressing (hot)	1500325000	Rice, flour	0.001
83101600	Bacon and tomato dressing	1500325000	Rice, flour	0.001
83102000	Caesar dressing	1500325000	Rice, flour	0.002
83103000	Coleslaw dressing	1500325000	Rice, flour	0.02
83107100	Mayonnaise, made with yogurt	1500325000	Rice, flour	0.005
83107200	Mayonnaise, made with tofu	1500323000	Rice, white	11.29
83108000	Mayonnaise, imitation	1500325000	Rice, flour	0.1
83108100	Mayonnaise, imitation, cholesterol free	1500325000	Rice, flour	0.01
83110000	Mayonnaise-type salad dressing	1500325000	Rice, flour	0.02
83110010	Mayonnaise-type salad dressing, cholesterol-free	1500325000	Rice, flour	0.001
83201200	Blue or roquefort cheese dressing, reduced calorie, fat-free, cholesterol-free	1500325000	Rice, flour	0.34
83202010	French dressing, reduced calorie, fat-free, cholesterol-free	1500325000	Rice, flour	0.01
83203250	Mayonnaise-type salad dressing, fat-free	1500325000	Rice, flour	0.03
83204000	Mayonnaise, low-calorie or diet	1500325000	Rice, flour	0.1
83204010	Mayonnaise, low-calorie or diet, low sodium	1500325000	Rice, flour	0.1
83204020	Mayonnaise, reduced calorie or diet, cholesterol-free	1500325000	Rice, flour	0.03
83204060	Mayonnaise-type salad dressing, low-calorie or diet, cholesterol-free	1500325000	Rice, flour	0.08
83210250	Creamy dressing, made with sour cream and/or buttermilk and oil, reduced calorie, cholesterol-free	1500325000	Rice, flour	0.04
91304250	Topping, milk chocolate with cereal	1500325000	Rice, flour	11.41
91351020	Topping, dietetic	1500325000	Rice, flour	0.02
91407150	Bean paste, sweetened	1500325000	Rice, flour	1.1

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
91510100	Gelatin powder, dietetic, sweetened with low calorie sweetener, dry	1500325000	Rice, flour	0.08
91511010	Gelatin dessert, dietetic, sweetened with low calorie sweetener	1500325000	Rice, flour	0.002
91511020	Gelatin dessert, dietetic, with fruit, sweetened with low calorie sweetener	1500325000	Rice, flour	0.001
91511030	Gelatin dessert, dietetic, with whipped topping, sweetened with low calorie sweetener	1500325000	Rice, flour	0.15
91511090	Gelatin dessert, dietetic, with fruit and vegetable(s), sweetened with low calorie sweetener	1500325000	Rice, flour	0.001
91511110	Gelatin dessert, dietetic, with fruit and whipped topping, sweetened with low calorie sweetener	1500325000	Rice, flour	0.01
91611100	Ice pop, sweetened with low calorie sweetener	1500325000	Rice, flour	0.02
91703050	Caramel with nuts and cereal, chocolate covered	1500325000	Rice, flour	17.91
91703400	Whatchamacallit	1500325000	Rice, flour	19.42
91705020	Milk chocolate candy, with cereal	1500325000	Rice, flour	16.3
91705420	Chocolate, white, with cereal	1500325000	Rice, flour	14.37
91715300	100 GRAND Bar	1500325000	Rice, flour	21.74
91745100	Skittles	1500325000	Rice, flour	0.03
91780010	Snickers Marathon Energy bar	1500324000	Rice, brown	7.54
91780010	Snickers Marathon Energy bar	1500325000	Rice, flour	0.16
91781010	Snickers Marathon Protein bar	1500324000	Rice, brown	7.54
91781010	Snickers Marathon Protein bar	1500325000	Rice, flour	0.16
92121030	Coffee and cocoa (mocha), made from powdered instant mix, with whitener and low calorie sweetener	1500325000	Rice, flour	0.01
92121040	Coffee, made from powdered instant mix, with whitener and low calorie sweetener	1500325000	Rice, flour	0.02
92121050	Coffee and cocoa (mocha), made from powdered instant mix, with whitener and low calorie sweetener, decaffeinated	1500325000	Rice, flour	0.01
92153100	Coffee, decaffeinated, with cereal	1500325000	Rice, flour	0.001
92192040	Coffee and cocoa (mocha) mix, dry instant powder, with whitener and low calorie sweetener, decaffeinated	1500325000	Rice, flour	0.32
92193020	Coffee, dry instant powder, with whitener and low calorie sweetener	1500325000	Rice, flour	0.55
92203000	Cereal beverage	1500325000	Rice, flour	0.004
92205000	Rice beverage	1500324000	Rice, brown	14.91
92301080	Tea, NS as to type, presweetened with low calorie sweetener	1500325000	Rice, flour	0.006
92301180	Tea, NS as to type, decaffeinated, presweetened with low calorie sweetener	1500325000	Rice, flour	0.006
92305090	Tea, made from powdered instant, presweetened with low calorie sweetener	1500325000	Rice, flour	0.006
92305110	Tea, made from powdered instant, decaffeinated, presweetened with low calorie sweetener	1500325000	Rice, flour	0.006
92520910	Lemonade, low calorie	1500325000	Rice, flour	0.03
92531020	Orange breakfast drink, made from frozen concentrate	1500325000	Rice, flour	0.001
92541020	Lemonade-flavored drink, made from powdered mix, with sugar	1500325000	Rice, flour	0.001
92541040	Lemonade-flavored drink, made from powdered mix, low calorie	1500325000	Rice, flour	0.002
92542000	Fruit flavored drink, made from powdered mix,with high vitamin C	1500325000	Rice, flour	0.008
92552010	Fruit flavored drink, made from powdered mix, low calorie	1500325000	Rice, flour	0.16
92611510	Horchata beverage, made with rice	1500323000	Rice, white	1.29
92731000	Fruit-flavored drink, non-carbonated, made from powdered mix, with sugar	1500325000	Rice, flour	0.001

WWEIA Food Code	WWEIA Food Description	FCID Code	FCID Desc	Commodity%
92741000	Fruit-flavored drink, non-carbonated, made from low calorie powdered mix	1500325000	Rice, flour	0.001
92751000	Root beer, noncarbonated, made from powdered mix, with sugar	1500325000	Rice, flour	0.001
92900100	Tang, dry concentrate	1500325000	Rice, flour	0.06
92900110	Fruit-flavored beverage, dry concentrate, with sugar, not reconstituted	1500325000	Rice, flour	0.01
92900200	Fruit-flavored beverage, dry concentrate, low calorie, not reconstituted	1500325000	Rice, flour	0.16
93101000	Beer	1500323000	Rice, white	4.14
93102000	Beer, lite	1500323000	Rice, white	4.14
93401100	Wine, rice	1500323000	Rice, white	24.44
94100300	Water, fruit flavored, sweetened, with high fructose corn syrup and low calorie sweetener	1500325000	Rice, flour	0.14

9.9.2 NHANES/WWEIA FOOD CODES USED IN ESTIMATES OF RICE INTAKES PER EATING OCCASION

Table 9.22. Brown Rice Food Codes

WWEIA Food Code	WWEIA Food Description
56205110	Rice, brown, cooked, regular, fat not added in cooking
56205120	Rice, brown, cooked, regular, NS as to fat added in cooking
56205510	Rice, brown, cooked, regular, fat added in cooking
56205530	Rice, brown, cooked, instant, NS as to fat added in cooking
56205540	Rice, brown, cooked, instant, fat not added in cooking
56205550	Rice, brown, cooked, instant, fat added in cooking

Table 9.23. White Rice Food Codes

WWEIA Food Code	WWEIA Food Description
56204980	Rice, white, cooked, converted, NS as to fat added in cooking
56204990	Rice, white, cooked, regular, NS as to fat added in cooking
56205010	Rice, white, cooked, regular, fat not added in cooking
56205020	Rice, white, cooked, instant, NS as to fat added in cooking
56205030	Rice, white, cooked, instant, fat not added in cooking
56205040	Rice, white, cooked, converted, fat not added in cooking
56205190	Rice, white, cooked, glutinous
56205410	Rice, white, cooked with (fat) oil, Puerto Rican style (Arroz blanco)
56205420	Rice, white, cooked, regular, fat added in cooking
56205430	Rice, white, cooked, instant, fat added in cooking
56205440	Rice, white, cooked, converted, fat added in cooking

Table 9.24. Baby Food Rice Food Codes, Infants Ages 0 - 1 y Only

WWEIA Food Code	WWEIA Food Description
57805000	Rice cereal, baby food, dry, instant
57805080	Rice cereal with apples, baby food, dry, instant
57805100	Rice cereal with bananas, baby food, dry, instant
57805500	Brown rice cereal, baby food, dry, instant
57820100	Rice cereal, baby food, jarred, NFS
57824000	Rice cereal with applesauce and bananas, baby food, jarred
57824500	Rice cereal with mixed fruit, baby food, jarred

9.10 ESTIMATES OF RICE INTAKE: FACTORS FOR ASSESSING INTAKE FREQUENCY

Table 9.25. Factors for Converting Rice/Cooked Grain Consumption per Year, Month, Week to Times per Day

Frequency Category[a]	Factor for converting consumption times per year, month, or week to times per day
Never	0
1-6 times per year	3.5/365
7-11 times per year	9/365
1 time per month	1/31
2-3 times per month	2.5/31
1 time per week	1/7
2 times per week	2/7
3-4 times per week	3.5/7
5-6 times per week	5.5/7
1 time per day	1
2 or more times per day	2

[a] Possible responses to question FFQ0058 ("How often did you eat rice or other cooked grains (such as bulgur, cracked wheat, or millet)?"), National Health and Nutrition Examination Survey (NHANES), 2003-2004 and 2005-2006, Food Frequency Questionnaire.

9.11 ESTIMATES OF RICE INTAKE: PER CAPITA PER DAY AND PER EATING OCCASION

Table 9.26. Consumption of Rice from Infant Rice cereals: Males and Females Less Than 1 Year of Age

Infant Rice Cereal Type	NHANES/ WWEIA Survey Years	Total n (unwgtd)	n eaters (unwgtd)	% eaters	2-day average Mean per capita[a] g/day	Equivalent tablespoons dry infant rice cereal[b]	2-day average Mean per capita[a] g/kg bw/day
All	2009-10	361	115	31.4	4.3	1.7	0.531
All	2003-10	1611	555	37.3	5.0	2.0	0.664
Brown	2003-10	1611	5	0.2	< 0.1[c]	—	0.003[c]
White	2009-10	361	113	31.1	4.3	1.7	0.525
White	2003-10	1611	552	37.2	5.0	2.0	0.661

[a] Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population response rates. All estimates exclude breast feeding children. n=sample size.

[b] Assumes 1 tablespoon baby cereal = 2.5 g (USDA, 2013).

[c] Estimates may not be statistically reliable due to small number of eaters.

Table 9.27. Consumption of Rice (including rice flour) from All Sources: Males and Females Less Than 1 Year of Age

Rice Type	NHANES/ WWEIA Survey Years	Total n (unwgtd)	n eaters (unwgtd)	% eaters	2-day average Mean per capita[a] g/day	Equivalent tablespoons dry infant rice cereal[b]	2-day average Mean per capita[a] g/kg bw/day
All	2009-10	361	202	55.8	6.3	2.5	0.739
All	2003-10	1611	992	65.0	7.4	3.0	0.924
Brown	2009-10	361	16	5.5	0.4[c]	0.1[c]	0.037[c]
Brown	2003-10	1611	51	5.5	0.4[c]	0.2[c]	0.041[c]
White (incl. rice flour)	2009-10	361	201	55.7	5.9	2.4	0.702
White (incl. rice flour)	2003-10	1611	986	64.7	7.0	2.8	0.883

[a] Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population response rates. n=sample size.

[b] Assumes 1 tablespoon baby cereal = 2.5 g (USDA, 2013).

[c] Estimates may not be statistically reliable due to small number of eaters.

Table 9.28. Consumption of Rice (including rice flour) from All Sources: Males and Females, 0 – 6 years and 0 – 50 years

Rice Category	Population group	NHANES/ WWEIA Survey Years	Total n (unwgtd)	n eaters (unwgtd)	% eaters	2-day average Mean per capita[a] g/day	Equivalent cups prepared rice[b,c]	2-day average Mean per capita[a] g/kg bw/day
All	MF 0 – 6 y	2009 – 2010	1477	1198	84.1	8.4	0.2	0.566
All	MF 0 – 6 y	2003 – 2010	6081	4965	84.8	7.8	0.1	0.556
All	MF 0 – 50 y	2009 – 2010	6013	5281	88.9	18.8	0.3	0.332
All	MF 0 – 50 y	2003 – 2010	24471	21263	88.7	16.8	0.3	0.304
Brown	MF 0 – 6 y	2009 – 2010	1477	118	10.8	0.7	< 0.1	0.047
Brown	MF 0 – 6 y	2003 – 2010	6081	285	6.1	0.7	< 0.1	0.048
Brown	MF 0 – 50 y	2009 – 2010	6013	511	11.3	1.7	< 0.1	0.029
Brown	MF 0 – 50 y	2003 – 2010	24471	1345	7.2	1.0	< 0.1	0.021
White (incl. rice flour)	MF 0 – 6 y	2009 – 2010	1477	1188	83.4	7.6	0.1	0.519
White (incl. rice flour)	MF 0 – 6 y	2003 – 2010	6081	4930	84.2	7.1	0.1	0.508
White (incl. rice flour)	MF 0 – 50 y	2009 – 2010	6013	5231	88.0	17.1	0.3	0.303
White (incl. rice flour)	MF 0 – 50 y	2003 – 2010	24471	21101	87.9	15.8	0.3	0.284

[a] Data source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Food codes included in analysis are listed in Appendix 9.9.2. Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population response rates. M = Males; F = Females; n=sample size.

[b] Assumes ratios of cooked:raw rice of 3.4 and 2.9 for brown and white rice, respectively.

[c] Assumes cup weights of 195 and 158 for prepared brown and white rice, respectively (USDA, 2013).

Table 9.29. Consumption of Dry Infant Rice Cereal by Males and Females Less Than 1 Year of Age per Eating Occasion

NHANES/ WWEIA survey years	total n (unwgtd)	n eaters (unwgtd)	Mean dry rice cereal intake[a] g/eating occasion	Mean dry rice cereal intake[a] tablespoons/ eating occasion	Mean dry rice cereal intake[a] g/kg bw/eating occasion
2009 – 2010	361	115	9.6	3.8	1.174
2003 – 2010	1611	555	8.6	3.4	1.125

[a] Data Source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Analyses conducted using Food Analysis and Residue Evaluation (FARE) v. 10.05 (Durango Software, LLC). Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population response rates. n=sample size.

Table 9.30. Mean Consumption of Rice per Eating Occasion

Rice Type	Population group	NHANES/ WWEIA survey years	total n (unwgtd)	n eaters (unwgtd)	Cooked Rice[a,b] g/eating occasion	Cooked Rice[a,b] cups/eating occasion	Uncooked rice g/eating occasion	Cooked rice g/kg bw/eating occasion	Uncooked rice g/kg bw/eating occasion
Brown	MF 0 – 6 y	2009 – 2010	1477	24	53.4[c]	0.3[c]	15.7[c]	3.429[c]	1.010[c]
Brown	MF 0 – 6 y	2003 – 2010	6081	72	60.0	0.3	17.7	4.040	1.190
Brown	MF 0 – 50 y	2009 – 2010	6013	154	185.2	0.9	54.9	2.926	0.866
Brown	MF 0 – 50 y	2003 – 2010	24471	447	182.4	0.9	54.1	2.987	0.885
White (incl. rice flour)	MF 0 – 6 y	2009 – 2010	1477	213	92.6	0.6	32.0	5.576	1.929
White (incl. rice flour)	MF 0 – 6 y	2003 – 2010	6081	741	88.0	0.6	30.1	5.565	1.903
White (incl. rice flour)	MF 0 – 50 y	2009 – 2010	6013	940	172.6	1.1	59.9	3.152	1.094
White (incl. rice flour)	MF 0 – 50 y	2003 – 2010	24471	3201	164.1	1.0	56.2	3.121	1.071

[a] Data Source: National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2004, 2005-2006, 2007-2008, and 2009-2010. Analyses conducted using Food Analysis and Residue Evaluation (FARE) v. 10.05 (Durango Software, LLC). Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data to correct for differences in population response rates. M= Male; F= Female; n=sample size.

[b] Intakes from regular rice consumed alone (not part of a mixture); food codes included are listed in Appendix 9.9.2.

[c] Estimates may not be statistically reliable due to small number of eaters.

9.12 COMPARISON OF CURRENT STUDY RESULTS WITH INORGANIC ARSENIC EXPOSURE ESTIMATES FROM OTHER SOURCES

FDA participated in a study (Yost *et al.*, 2004) of inorganic arsenic intakes by children ages 1 – 6 years in a previous effort to characterize inorganic arsenic intake from rice and other foods in the U.S. In the 2004 study, which updated an even earlier exposure assessment (Yost *et al.* 1998), inorganic arsenic concentration data reported by Schoof *et al.* (1999) were combined with 1994 – 1996 and 1998 data from the USDA Continuing Survey of Food Intakes by Individuals (CSFII) to estimate total inorganic arsenic intakes and contributions to inorganic arsenic intake from specific food groups. Rice and rice products were estimated to contribute 19.8% of the mean total estimated inorganic arsenic intake of 3.2 µg/day, which translates to 0.6 µg inorganic arsenic intake from rice and rice products per day. In the current risk assessment, inorganic arsenic exposure from rice was estimated at 54.3 ng/kg bw/day for children ages 0 – 6. Based on an average body weight of 15 kg, the daily equivalent inorganic arsenic exposure from rice is 0.8 µg/day.

As noted in Section 4.2.1, under contract with FDA, Oak Ridge National Laboratory searched the scientific literature to identify studies reporting inorganic arsenic exposure from rice intake in the U.S. No relevant U.S. studies were identified. However, several reports were identified on inorganic arsenic exposure from rice in countries other than the U.S.

The inorganic arsenic exposures estimated in the identified foreign studies are higher than those estimated in the current risk assessment. In some cases, this is because the mean inorganic arsenic concentrations in rice are higher than those found in the U.S., but in most cases the relatively high estimates of inorganic arsenic intake from rice reflect higher average rice intakes per day or per eating occasion by the populations studied.

Meharg *et al.* (2008) analyzed 17 baby rice products sold in the UK and found a median inorganic arsenic concentration of 110 ppb (range: 60 – 160 ppb). Inorganic arsenic intake per eating occasion (20 g baby rice) was estimated at 2.2 µg; based on a reported average body weight of 9.25 kg for 1 year old babies, this is equivalent to 238 ng/kg bw/eating occasion, a level far above that estimated for infants or either of the other life stages addressed in the current risk assessment.

Fontcuberta *et al.* (2011) measured inorganic arsenic (iAs) in rice obtained from retail locations in Barcelona, Spain. The mean iAs concentration in 23 white rice samples was 120 ppb, a level higher than the mean concentrations found by FDA or Consumer Reports in U.S. samples. Exposure to iAs from rice was estimated using results of the Catalan Nutrition Survey (ENCAT). The mean iAs intake from rice and rice products in Catalan was estimated as 3.73 µg/day, or 53.3 ng/kg bw/day based on an assumed mean adult body weight of 70 kg. This level of intake is

substantially higher than the 31.8 ng/kg bw/day estimated in the current study for ages birth through 50 years.

Batista *et al.* (2011) estimated that on average, Brazilians consume 88 g rice per day. Based on inorganic arsenic concentrations measured in 44 rice samples obtained through nationwide sampling, mean inorganic arsenic intake from rice in Brazil was estimated at 11.17 µg/day, or 160 ng/kg bw/day based on a mean body weight of 70 kg.

Li *et al.* (2011) used results of the China National Nutrition and Health Survey (CNNHS) and inorganic arsenic concentration data from the published literature to estimate that inorganic arsenic intake from rice in China averages 24.5 µg/day, or 409 ng/kg bw/day based on a mean body weight of 60 kg.

In Thailand, where the average daily consumption of milled rice has been estimated at 276 g/day, mean inorganic arsenic intakes from white rice were estimated as 2.618 µg/kg bw/week, and inorganic arsenic intakes from colored rice (brown, black, and red) were estimated as 3.754 µg/kg bw/week (Nookabkaew *et al.*, 2013). These intakes are equivalent to 374 ng/kg bw/day from white rice and 536 ng/kg bw/day for colored rice, for a total inorganic arsenic exposure of 910 ng/kg bw/day from rice intake.

Phan *et al.* (2013) found that inorganic arsenic intake from rice in the Mekong River basin of Cambodia varied regionally due to wide variation in inorganic arsenic concentrations in rice. Mean inorganic arsenic concentrations in rice (n=10 in each region) were 204 ppb in the Kandal region (range: 8 – 951 ppb), 64 ppb in the Kratie region (range: 4 – 152), and 10 ppb in the Kampong Cham region (range: 3 – 25 ppb). Based on the assumptions that Cambodians eat a total of 450 g uncooked rice per day, and that the average body weight is 52 kg, mean inorganic arsenic intakes from rice were estimated as 1765 ± 2374 ng/kg bw/day in the Kandal region, 550 ± 398 ng/kg bw/day in the Kratie region, and 86 ± 74 ng/kg bw/day in the Kampong Cham region.

In conclusion, the mean per capita inorganic arsenic exposure from rice in the U.S. is relatively low compared with those reported in other countries, due at least in part to relatively low per capita consumption of rice.

9.13 NON-CANCER HEALTH EFFECTS LITERATURE REVIEW

Research Studies Considered for Effects of Arsenic on Development during Pregnancy

A number of epidemiology studies have been conducted to determine the association between inorganic arsenic exposure and adverse pregnancy outcomes in several areas around the world. In many areas, the main source of drinking and cooking water is tube wells where arsenic levels are elevated. As stated previously in this report, the majority of arsenic in water is in the form of inorganic arsenic. Inorganic arsenic exposure was assessed by different methodologies in these studies including the analysis of total arsenic (regularly reported as "arsenic") and/or arsenic species, arsenic in maternal urines collected at various stages of pregnancy, or by looking at the average and/or range of arsenic levels in tube wells available to the studied populations. Pregnancy outcomes that were addressed included stillbirths, spontaneous abortion, term low birth size, infectious disease susceptibility, and pre-term birth. All studies discussed below were controlled or adjusted for as many biologically important covariates as possible to avoid biases, and applied appropriate statistical analyses.

Rahman *et al.* (2007, 2009, 2010) conducted several prospective population-based cohort studies on pregnancies identified by the health and demographic surveillance system in Matlab, Bangladesh, a rural farming area, using data obtained from the health and demographic surveillance system carried out by International Centre for Diarrheal Disease Research, Bangladesh. The Center has been running this surveillance system in the Matlab area since 1996 and covers a population of about 220,000. (Rahman *et al.*, 2007, 2009, 2010).

Rahman *et al.* (2007) conducted a large study involving a cohort of 29,134 pregnancies during 1991 – 2000 in Matlab to evaluate the association between arsenic exposure via drinking water and fetal and infant survival. Arsenic exposure was estimated by drinking water history and analysis of arsenic concentrations in tube wells. The investigators found that drinking tube water with more than 50 µg/L of arsenic during pregnancy significantly increased, in a dose-response manner, the risks of fetal loss and infant death.

Rahman *et al.* (2009) evaluated the association of prenatal arsenic exposure with size at birth, including birth weight, birth length, head or chest circumferences for 1,578 mother–infant pairs. Arsenic exposure was estimated by analysis of arsenic in urine collected at approximately 8 and 30 weeks of gestation. No dose-effect association was observed between arsenic exposure and birth weight or length, head circumference, or chest circumference over the full range (6 – 978 µg/L) of arsenic exposure. The investigators did report that in the range of arsenic exposure of 0 – 100 µg/L, each 1 µg/L increase in urinary arsenic concentration was associated with a 1.68-gram reduction in birth weight. This effect leveled out after 100 µg/L and above.

Rahman *et al.* (2010) evaluated the association of arsenic exposure, as assessed by arsenic concentrations in the urine at week 8 and 30 of gestation, with spontaneous abortion, still birth and infant mortality in 2,924 pregnant women. The urinary arsenic concentration was adjusted by specific gravity; many of the studied women suffered from malnutrition so the more commonly-used creatinine adjustment was not appropriate. Women were divided into 5 groups with a median arsenic exposure of 23, 42, 80, 177, and 382 µg/L, respectively. The investigators observed a clear increase in infant mortality with increasing prenatal arsenic concentrations. However, there was no statistically significant evidence of increased risks of spontaneous abortions or still births.

Rahman *et al.* (2011) evaluated the association between arsenic exposure during pregnancy and morbidity during infancy in 1,552 live-birth infants, a subset of the cohort used for the Rahman *et al.* (2010) study. Arsenic exposure was calculated by the concentrations of maternal metabolites of inorganic arsenic in the maternal urine samples collected at gestational week 8 and 30. Information on symptoms of lower respiratory tract infections and diarrhea in infants was collected by 7-day recalls at monthly home visits. Arsenic exposure during pregnancy was associated with increased infant morbidity due to infectious diseases for mothers in the highest exposure group (262 – 977 µg/L) compared to the lowest exposure group (< 39 µg/L).

Huyck *et al.* (2007) recruited 52 pregnant women in rural Bangladesh for a pilot study to examine the effects of maternal arsenic exposure on birth weight. Hair, toenail, and drinking water samples were collected at multiple points during pregnancy and from newborns to estimate arsenic exposure. The investigators found that higher maternal hair arsenic measured in early pregnancy was associated with lower birth weights. For every 1 µg/g increase in hair arsenic, birth weight decreased by 194 g.

Milton *et al.* (2005) conducted a cross-sectional study of 533 pregnant women exposed to varying arsenic concentrations in drinking water to examine the risks of spontaneous abortions, stillbirths, and neonatal deaths. Subjects lived in different rural districts of Bangladesh. Arsenic exposure was characterized by a single well-water measurement for each study subject. Five groups were looked at (1 – 30, 31 – 50, 51 – 100, 101 – 500, and > 500 µg/L). The investigators found a significant association between concentrations of arsenic in the water > 50 µg/L (approximately 0.006 mg As/kg/day) and spontaneous abortion and stillbirth but not neonatal death.

Cherry *et al.* (2008) conducted a retrospective analysis on the outcome of 30,984 deliveries of babies born in rural Bangladesh to estimate the association of stillbirths with exposure to arsenic in the drinking water. An increased risk of stillbirth was associated with exposure to arsenic at 50 µg/L or greater, after adjustment for 17 socioeconomic and health factors.

Kwok *et al.* (2006) examined pregnancy outcome data for 2,189 women obtained from the Bangladesh Rural Advancement Committee administered Community Nutrition Centers, which provide care to all pregnant women chronically exposed to a range of concentrations of arsenic in drinking water. The study examined associations with selected adverse reproductive outcomes, such as stillbirths, birth defects, and low birth weights. Arsenic exposure was estimated from drinking water samples from tube wells and ranged from ND to >300 µg/L. This study found a small association between arsenic exposure and all birth defects, including individual cases of cleft lip and palate, anencephaly and hydrocephalus, congenital heart disease, missing hand, laryngomalacia, three cases of club feet, and two cases of neural tube defects or meningocele. No other outcomes were significantly associated with arsenic in drinking water. There were very few birth defects observed, 11 cases total. There was no follow-up described to look for defects that may not be evident until six months after birth.

Ahmad *et al.* (2001) compared pregnancy outcomes of women living in rural Bangladesh who were exposed to arsenic-contaminated water with those who were not. Both control and exposed subjects were matched across a large number of variables. Ninety-six women were in each group. In the exposed group, 98% were exposed for 5 – 10 years to drinking water with arsenic higher than 10 µg/L. Adverse pregnancy outcomes such as spontaneous abortions, stillbirths, and preterm birth rates were significantly higher in the exposed group.

Mukherjee *et al.* (2005) carried out a detailed study of 25,274 people from arsenic-infected districts in West Bengal, India. A subset of 17 pregnant women were looked at as part of a pilot study; Group A (n = 6) was exposed to 284 – 400 µg/L arsenic in drinking water; Group B (n = 11) was exposed to 401 – 1474 µg/L as determined by measurements of arsenic in water from the tube wells. The respondents were compared on the basis of duration of drinking arsenic-contaminated water into two categories, either drinking water elevated in arsenic for 5 – 10 years or for more than 10 years. Although a very small set of women were observed, rates of spontaneous abortion, low birth weight, and neonatal death was significantly higher for respondents having longer exposure.

Sen and Chaudhuri (2008) assessed the role of arsenic on the incidence of stillbirths and miscarriages among 240 pregnant women exposed to arsenic through contaminated drinking water in several districts in West Bengal, India compared to 60 control women from a village where arsenic contamination was low. Women were matched for many covariates. Women exposed to ≥ 60 µg/L had higher incidences of stillbirths and miscarriages compared to controls (<0.01 µg/L).

von Ehrenstein *et al.* (2006) conducted a study of 202 women from West Bengal, India, and reported that exposure to arsenic concentrations of arsenic ≥ 200 µg/L in drinking water during

pregnancy was associated with a 6-fold increased risk of stillbirth. No association was found between arsenic exposure and risk of spontaneous abortion.

Guan *et al.* (2012) evaluated the effects of exposure to arsenic on birth size in a cross-sectional study of 125 mother-infant pairs in Dalian, a moderate sized industrial city in China. Arsenic exposure was determined by measurements of maternal and cord blood. Mean values in maternal blood and cord blood were 6.9 and 5.4 µg/L respectively. Since cord blood was significantly lower than maternal blood in arsenic, the investigators postulated that the placenta prevented part of the maternal arsenic from entering the fetal body. However, their data also suggested that the barrier function of the placenta may decrease with increasing maternal concentrations and that maternal exposure to environmental levels of arsenic may be associated with impaired fetal growth. Fetal arsenic concentration was negatively associated with head circumference.

Myers *et al.* (2010) analyzed data from routine prenatal and postpartum examinations of pregnant women and their infants in Mongolia, China. Exposure to arsenic was calculated from information from an existing database of well-water arsenic concentrations. The study did not show an association between maternal drinking water arsenic exposure and adverse birth outcomes but did find a two-fold increased risk for neonatal death for arsenic above the Chinese drinking water standard of 50 µg/L.

Hopenhayn-Rich *et al.* (2000) compared the rates of stillbirths and infant mortality for the time period 1950 – 1996 between two Chilean cites, Antofagasta and Valparaiso; one with historically high levels of arsenic and one with low levels. In Antofagasta, arsenic levels in groundwater ranged from 97 µg/L during the 1950s, then up to 860 µg/L during the period 1958 – 1970, then dropping to 110 µg/L by 1979 and finally to 40 µg/L by 1996. The results suggested that exposure to inorganic arsenic may be associated with an increase in infant mortality after adjustment for known confounders. All infant mortality endpoints (late fetal, neonatal, and postnatal) showed a dramatic decrease over time, with decreasing arsenic concentration in drinking water.

Hopenhayn *et al.* (2003) conducted a prospective cohort study of newborns in Antofagasta and Valparaiso, with moderate (40 µg/L) and low (< 1 µg/L) levels of arsenic in water to examine the effects on birth weight. About 400 infants were in each group (424 in the moderate group; 420 in the low group). Investigators found that, after adjusting for confounders, moderate arsenic exposures during pregnancy from drinking water were associated with a reduction in birth weight.

Raqib *et al.* (2009), in a study of 140 Bangladeshi women, reported correlations between maternal urinary arsenic and the health of the mother (fever, diarrhea during and acute respiratory infections during pregnancy) and infant thymic size and morbidity, particularly

evident in male children. Furthermore, arsenic exposure significantly negatively correlated with interleukin-7 and lactoferrin in breast milk.

Saha *et al.* (2012) measured arsenic species in mothers' urine in late pregnancy for 2,372 Bangladeshi infants and found an inverse correlation between arsenic urinary metabolites and children's weight at 3 – 24 months. This finding was more robust at a later age, particularly for girls. There is increasing evidence that early-life arsenic exposures affecting fetal and infant growth, mainly by epigenetic effects, may cause chronic disease later in life (Godfrey and Barker, 2000; Langley-Evans, 2006). Arsenic has been shown to both affect fetal growth and to cause epigenetic effects (Vahter, 2007; Vahter, 2008).

The most important epigenetic events observed after exposure to inorganic arsenic are: (i) hypermethylation of DNA gene promoters; (ii) loss of global DNA methylation, and (iii) alteration of global histone H3 methylation (EFSA, 2009).

An epigenetic DNA methylation study was conducted on cord bloods from 134 New Hampshire, US infants at birth. In this study, maternal urine was measured at weeks 24 – 28 of gestation for inorganic arsenic content (Koestler *et al.*, 2013). It was found that DNA methylation was increased in babies whose mothers had higher urinary inorganic arsenic compared to the lowest group. This suggests that low-level inorganic arsenic exposure has an impact on the epigenome as urinary inorganic arsenic ranged only from 0.13 – 0.45 µg/L. The range of tap water arsenic consumed by mothers was 0.2 – 6.2 µg/L. As only DNA methylation was studied, no links to the children's health was made. A related study that quantified gene expression in placental tissue, but with maternal drinking water ranging from 0.2 – 3.55 µg/L arsenic and maternal urinary total arsenic ranging from 1.8 – 11.9 µg/L (inorganic arsenic levels not given) found that arsenite transporting aquaporin (AQP9) expression levels were correlated with urinary arsenic levels (Fei *et al.*, 2013). Furthermore, AQP9 itself was related negatively to the expression of a phospholipase (ENPP2) whose expression was positively correlated with birth weight. The conclusions from this study were that there was a suggestion that even low inorganic arsenic exposure levels may affect birth weight.

In a study of 229 women urine was sampled at a 6 month pre-natal visit along with a 3 day dietary record and a sample of tap water for arsenic testing (Gilbert-Diamond *et al.*, 2011). Both rate of rice consumption and tap water arsenic were significantly correlated with both total urinary arsenic and with urinary inorganic arsenic.

Research Studies Considered for Effects of Arsenic on Health and Development during Infancy and Early Childhood

Exposure to inorganic arsenic has been demonstrated to have neurologic consequences in adults (ATSDR, 2012) and evidence is growing that demonstrates neurological consequence in children's intellectual function. Children appear to be particularly susceptible to neurotoxic effects as suggested by findings on lead, methylmercury, and polychlorinated biphenyls (PCBs). Children three years of age and younger are the most exposed to inorganic arsenic as they have 2 – 3 fold higher intakes of food on a per body mass basis as compared to adults (EFSA, 2009). Additionally, brain growth in children is about 90% that of an adult by 6 year of age. Perturbation from exposure to exogenous chemicals assessment during this period of rapid development may lead to later adverse health effects.

Infants appear to have lower exposure to arsenic during the breast-feeding period because the passage of arsenic through the mammary gland is limited. In contrast, formula prepared from drinking water may result in a very high exposure, depending on level of arsenic in the water (EFSA, 2009).

Wasserman *et al.* (2004) conducted a cross-sectional evaluation of intellectual function in 201 children, 10 years of age, whose parents were part of a larger cohort in Bangladesh. Intellectual function was measured using tests drawn from the Wechsler Intelligence Scale for Children. Results were assessed by summing related items into Verbal, Performance, and Full-Scale raw scores. Water arsenic concentration of tube wells at each child's home was obtained by surveying all wells in the region. Urinary arsenic and blood lead were also measured in the children. The mean total arsenic concentration in the water was 118 µg/L. The children were divided into four exposure groups, representing < 5.5, 5.6 – 50, 50 – 176, or 177 – 790 µg As/L drinking water. After adjustment for confounding factors, a dose-related inverse effect of arsenic exposure was seen on both Performance and Full-Scale subset scores; for both end points, exposure to ≥ 50 µg/L resulted in statistically significant differences relative to the lowest exposure group (< 5.5 µg/L).

In another study, Wasserman *et al.* (2007) expanded their research to examine 301 6-year-old children from the same area. In this case, the children were categorized into the following quartiles based on water arsenic concentration: 0.1 – 20.9, 21 – 77.9, 78 – 184.9, and 185 – 864 µg/L. After adjustment for water manganese (Mn), blood lead, and socio-demographic features known to contribute to intellectual function, water derived arsenic was significantly negatively associated with both Performance and Processing speed raw scores. Analyses of the dose-response showed that compared to the first quartile, those in the second and third categories had significantly lower Performance raw scores. Those in the fourth category had marginally significantly lower Full-Scale and Processing Speed raw scores.

The results from Wasserman *et al.* (2004, 2007) are consistent with those of ecological studies in children in Taiwan (Tsai *et al.*, 2003). Adolescents exposed to low (1.7 – 1.8 µg iAs/kg/day; n = 20) levels of inorganic arsenic in the drinking water showed decreased performance in the

switching attention task, while children in the high exposure group (3.4 – 4.2 µg iAs/kg/day; n = 29) showed decreased performance in both the switching attention task and in tests of pattern memory, relative to unexposed controls (n = 60).

Hamadani *et al.* (2010) conducted a longitudinal cohort study beginning in early pregnancy in rural Bangladesh. The investigators assessed the effects of pre- and postnatal arsenic exposure on development of 2,112 children at 18 months of age. Median maternal urinary arsenic concentration averaged over early and late gestation (9 and 30 weeks) was 96 µg/L and children's urine was 35 µg/L. They found no significant effects of any arsenic exposures on any child development measurement at 18 months.

Hamadani *et al.* (2011) conducted an additional population-based longitudinal study of cognitive function in rural Bangladesh with 1700 children at 5 years of age. Median maternal arsenic concentration in pregnancy, measured in urine at gestational weeks 8 and 30, was 80 µg/L and children's urine at 5 years contained 51 µg/L. Using the Wechsler Intelligence Scale for Children, the investigators found that verbal IQ and full scale IQ was significantly adversely affected with increasing arsenic exposure in girls, but not in boys.

von Ehrenstein *et al.* (2007) conducted a cross-sectional study among 351 children aged 5 – 15 years of age in West Bengal, India to assess the effects of exposure to inorganic arsenic on childhood intellectual function. Arsenic exposure was measured by arsenic urine concentrations and an assessment of lifetime exposure to arsenic in drinking water. The investigators found significant associations between current urinary arsenic concentrations and reductions in scores of tests of vocabulary, object assembly, and picture completion; the magnitude of the reductions varied between 12% and 21%. In this cohort, the average lifetime peak arsenic concentration in well water was 147 µg/L.

A large population-based cohort study looked at the effects of *in utero* arsenic exposure via drinking water on infant development at 7 months of age. Exposure was assessed by arsenic in maternal urine in early and late pregnancy. This study was conducted in an area with a high prevalence of arsenic-contaminated tube wells in rural Bangladesh (Tofail *et al.*, 2009). Measurements of problem-solving ability and motor development (Bayley Scales of Infant Development-II) among 1,799 infants were not related to prenatal arsenic exposure in multiple regressions of children's motor and problem-solving test scores and behavior ratings, after controlling for socioeconomic background variables, age, and sex. However, it is possible that effects other than those measured occurred, or that effects may become apparent at a later age since most children were breast-fed and thus not exposed to high levels of arsenic-contaminated water. Both Tofail *et al.* (2009) and Hamadani *et al.* (2011) postulated that neurotoxic effects might become apparent later in childhood when children were no longer breast-fed and were, therefore, exposed to increased concentrations of arsenic in water.

In the Wang *et al.*, (2007) study in China, 87 children (age 8 – 12 years), 87 whose mean arsenic concentration in the drinking water was 190 µg/L had a mean IQ score of 95 compared with 101 for children (n = 253) with 142 µg/L arsenic in the water and 105 for control children (n = 196) with 2 µg/L arsenic in the drinking water. The differences in IQ scores between the two exposure groups and the control group were statistically significant.

Dong and Su (2009) conducted a meta-analysis between arsenic exposure and children's intelligence to determine if arsenic exposure negatively affects IQ. Four Chinese cross-sectional studies that assessed the development of low IQ in children who had been exposed to arsenic earlier in their lives were included in this assessment. The results showed and association between exposure to arsenic and children's IQ test results in China. Those living in a high arsenic area have about six fewer IQ points than those not exposed to arsenic.

9.14 CAUSAL DETERMINATION FRAMEWORK

Below is the causality table developed by EPA for its review of inorganic arsenic.

Table 9.31. Criteria for Causal Determination

Descriptor	Causal Determination Considerations
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (i.e., doses or exposures genereally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes multiple high-quality studies.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes multiple high-quality studies.

Descriptor	Causal Determination Considerations
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited. For example, (a) at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent; or (b) a well-conducted toxicological study, such as those conducted in the National Toxicology Program (NTP), shows effect in animal species.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quanity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations, are mutually consistent in not showing an effect at any level of exposure.

9.15 UPDATE AND DISCUSSION OF PERTINENT LITERATURE FROM OCTOBER 2013 – FEBRUARY 2015

This appendix summarizes pertinent literature published from October 2013 through February 2015. Please note, this is not meant to be an exhaustive literature review of all papers published during this time period.

The FDA Arsenic Risk Assessment Team implemented stopping rules that established flexible cut-off dates for the acceptance of new studies and data. The stopping rules are grounded in general principles regarding what constitutes both pivotal new evidence and a reasonable period of delay. FDA will delay the completion of an assessment only if it has either reviewed and/or is awaiting potentially pivotal evidence from further analysis or follow-up of a critical epidemiologic study or critical animal study that might impact its original conclusions.

The health effects of and exposure to inorganic arsenic is a very active research field that FDA was and is aware of and actively monitors ongoing research and publications. The critical issue we sought to answer in conducting these literature review updates is whether the more recent publications described below fundamentally call into question the conclusion of our risk assessment.

9.15.1 AN UPDATE OF THE LITERATURE ON ADVERSE EFFECTS OF INORGANIC ARSENIC EXPOSURE TO THE DEVELOPING FETUS AND TO YOUNG CHILDREN

Our literature search and analysis focused on the following questions:

1) Are there new data that do not support the findings that inorganic arsenic (iAs) is associated with adverse pregnancy outcomes?

2) Are there new data that would enable FDA to calculate a point of departure for adverse pregnancy outcomes?

3) Are there new data that do not support the finding that iAs is associated with adverse neurodevelopmental effects in children?

4) Are there new data that would enable FDA to calculate a point of departure/reference dose for adverse neurodevelopmental effects in children?

5) Are there any other non-cancer endpoints of significance that are emerging in the literature for pregnant women (the developing fetus), infants and children?

At the request of the FDA, Oak Ridge National Library conducted a search of the literature from October 2013 to February 2015. The following search strategy was employed: Search: (Strategies: As/adverse effects OR As/toxicity AND (infant OR child, preschool OR child) "Maternal Exposure"[Mesh]) AND Human [MH] AND "Arsenic"[Mesh] Filters: 5 years; Search: ((("Child"[Mesh]) OR "Infant"[Mesh]) OR "Child, Preschool"[Mesh]) AND ("Arsenic/adverse effects"[Mesh] OR "Arsenic/toxicity"[Mesh]) Filters: 5 years

Search results, including abstracts, were provided to FDA from the National Center for Biotechnology Information at the U.S. National Library of Medicine. Over 134 papers were initially identified. For research papers to be included in this review, the criteria used in the RA were also applied here:

- Focused on the effects of iAs exposure by the oral route

- Considered the health effects reported in epidemiology studies regardless of the country of origin

Below is a synopsis of the pertinent new papers identified. The papers were sorted into three main topics to coincide with the questions asked: Adverse Pregnancy Outcomes, Neurobehavioral Effects, and New Non-Cancer Endpoints of Concern for the Developing Fetus or Infants and Children.

9.15.1.1 ADVERSE PREGNANCY OUTCOMES

Human and animal studies now link a multitude of early-life hardships, including prematurity, low birth weight and toxic exposures to a wide array of adult-onset diseases. Timing of the insult appears to be an important factor in the consequences (Barrett, 2012).

Bloom *et al*., (2014) examined the impact of low-level (<10 µg/L) iAs in drinking water and spontaneous pregnancy loss in a case-control study conducted in Timis County, Romania. The cases were women with incident spontaneous pregnancy loss at 5-20 weeks gestation (n=150). The controls were women with ongoing pregnancies matched by gestational age, demographics, and socioeconomic and lifestyle factors (n=150). Drinking water samples were analyzed for iAs. The study reported no statistically significant association between exposure to low level of iAs in drinking water and spontaneous pregnancy loss before 20 weeks.

Epidemiological studies and animal models suggest that *in utero* arsenic exposure affects fetal health. A negative association is often observed between maternal arsenic ingestion and infant birth weight (Fei *et al.*, 2013). However, the molecular mechanisms by which arsenic causes adverse pregnancy outcomes remain elusive. Validated biomarkers would facilitate risk assessment for low level exposures during fetal life.

Chou *et al.* (2014) conducted research to elucidate the association between arsenic exposure and oxidative/methylated DNA damage in pregnant women and its association with birth outcomes. The purpose was to assess the effects from maternal iAs exposure and maternal oxidative and methylated DNA damage on the health status of newborns. A birth cohort of 299 pregnant-newborn pairs was recruited in Taiwan. Maternal urine samples were collected during the third trimester to measure iAs and metabolites. Birth weights and Apgar scores were recorded. Adverse birth outcomes and decreased Apgar scores were associated with increased maternal levels of iAs and N7-MeG, a DNA damage biomarker, in the general population. The researchers observed a significantly increased relative risk of low Apgar scores associated with maternal iAs urine levels. The researchers concluded that maternal N7-MeG levels might be a novel biomarker for monitoring fetal health related to arsenic.

Laine *et al.* (2015) also attempted to establish biomarkers of exposure to iAs using a prospective study of 200 pregnant women recruited from Gomez Palacio, Mexico. Concentrations of iAs in drinking water and maternal urinary concentrations of iAs, monomethylated arsenic (MMA), and dimethylated arsenic (DMA) were measured. Drinking water iAs concentrations for study subjects ranged from < 0.5-236 µg/L. The study suggested that metabolism of iAs may be more important than exposure alone. Higher urinary DMA: MMA ratios appeared to have a protective effect on the fetus. Urinary levels of MMA were positively correlated with detrimental effects including low birth weight, gestational age and newborn length.

Fei *et al*. (2013) aimed to increase the understanding of low-dose arsenic exposure on fetal health by identifying possible arsenic-associated fetal tissue biomarkers. Arsenic (As) concentrations were determined from the urine samples of a cohort of 133 pregnant women from New Hampshire who were part of the ongoing New Hampshire Birth Cohort Study. Demographic and lifestyle information was collected. Spot maternal urine samples were collected. Infant clinical data, including birth weights, were recorded from the newborns' medical records. Median arsenic concentration in household tap water was 0.36 µg/L and median maternal urine arsenic concentration was 4.4 µg/L (range = 1.8-11.9). These urine values were consistent with an exposure range previously observed for a nationally representative U.S. sample. Placental tissues were profiled for gene expression across a panel of candidate genes, including known arsenic regulated targets and genes involved in arsenic transport, metabolism, or disease susceptibility. Multivariable adjusted linear regression models were used to examine the relationship of candidate gene expression with arsenic exposure or with infant birth weight. Placental expression of AQP9 – an arsenic transporter – was associated with maternal arsenic exposure during pregnancy. AQP9 expression has been shown to enhance arsenic's effect on cultured cells presumably through increased arsenic uptake. The researchers found significant associations between AQP9 expression and five of the six arsenic-regulated genes whose increased expression has the potential to modulate the effect of arsenic on target cells, including infant birth weight. Placental expression of AQP9 could be used as a potential fetal biomarker for arsenic exposure and its effect on birth outcomes.

Quansah *et al*. (2015) conducted a systematic review and meta-analysis to examine the association between arsenic and adverse pregnancy outcomes. The researchers identified 23 articles, 16 of which were judged to have sufficient data for quantitative analysis. The majority of these papers are discussed in the RA. Arsenic in groundwater ≥ 50 µg/L was associated with increased spontaneous abortions, stillbirths, moderate risk of neonatal mortality and significant reduction in birth weights. The authors stated that the findings of the study need to be interpreted in light of limitations inherent in the original studies including failure of some studies to adjust for appropriate potential confounders of adverse pregnancy outcomes/infant mortality and differences in calculation of exposure in the different studies. The RA agreed with the finding of no apparent adverse health effects from iAs in water at concentrations below 50 µg/L. Because of the limitations outlined above and in the RA, these data were not rigorous enough to use as a point of departure for developing a risk level.

9.15.1.2 NEURODEVELOPMENTAL EFFECTS

Background: One in every six children in the world has a developmental disability and in most cases these disabilities affect the nervous system (Grandjean and Landrigan, 2006). The most common neurodevelopmental disorders include learning disabilities, sensory deficits, developmental delays, and cerebral palsy. An expert committee of the National Research Council

concluded that 25% of these disorders arise from interactions between environmental factors and individual susceptibility (Grandjean and Landrigan, 2006). The developing brain is much more susceptible to injury than the adult brain (Grandjean and Landrigan, 2006).

Wasserman *et al*. (2014) examined 272 children in grades 3 to 5 from three Maine school districts to look at the association between drinking water arsenic levels and intelligence. There were previous studies in different populations that suggested arsenic exposure may affect early development but there was little consistency in the specific components of child intelligence most affected. Although 581 families agreed to participate, exclusions for a multitude of reasons decreased the sample size to 272 children. Children with conditions known to affect intelligence were excluded from this study. Home water samples and children's toenail samples were collected. Potential covariates were addressed. Child intelligence was assessed with standardized testing while at school. Water samples were taken at the point of entry in the home and at the consumption point. Each family completed the HOME Inventory, a widely used semi-structured assessment that combines interview and direct observation. The researchers used linear regression analysis to estimate associations between arsenic in drinking water and child IQ. After adjusting for HOME scores, for maternal education and IQ, for school district and for the number of other children in the home, children exposed to drinking water from household wells with arsenic levels ≥ 5 µg/L showed significant reductions in Full Scale, Working Memory, Perceptual Reasoning and Verbal Comprehension Scores. Categories of drinking water exposure did not differ significantly but this might be a result of the very small sample size. With adjustment for other contributions, drinking water with arsenic levels ≥ 5 µg/L was associated with reductions of 4.5 to 6.5 points in most scores. A major limitation was that there was not a clear dose-response at the arsenic levels greater than 5 µg/L. The researchers suggested that this might be an important threshold. The strength of associations is similar to those observed with modest increases in blood lead, an established risk factor for decreased IQ.

9.15.1.3 NEW NON-CANCER ENDPOINTS OF CONCERN FOR THE DEVELOPING FETUS OR INFANTS AND CHILDREN

Background: Infectious diseases are the primary cause of mortality in young children (Farzan *et al.*, 2013). Even children born in industrialized countries like the US experience a high burden of infection-related morbidity and mortality especially before the age of one year--primarily from respiratory infections and diarrhea. Gestation is a critical period for immune development (Gluckman, 2012). A child's immune system is more sensitive than adults and the establishment of immune memory occurs in early childhood. Emerging evidence in the literature suggests that arsenic enhances susceptibility to infection by impacting multiple aspects of the immune system. Chronic exposure to inorganic arsenic is associated with development of inflammatory-related diseases (Duncan *et al.*, 2014).

Glutathione S-transferase omega 1-1 (GSTO1-1), which has been associated with iAs metabolism, is known to participate in inflammatory and apoptosis cellular responses (Escobar-Garcia *et al.*, 2012). Escobar-Garcia *et al*. (2012) recruited 128 subjects, including children, from the Mexican region of Coahuila for the study. Children ranged from 5-15 years of age. Drinking water and urine was collected and arsenic species determined. Venous blood was also drawn. The mean concentration of iAs in drinking water was 73.7 µg/L (27-130 µg/L range). The presence of two polymorphisms of GSTO1-1 significantly modified the expression of IL-8, a pro-inflammatory cytokine, and TNF alpha, which is also associated with an over-expression of certain tumor types. These results suggest an important role for GSTO1-1 in the inflammatory response and the apoptotic process and indicate that its two polymorphisms could increase the risk of developing inflammatory and apoptosis-related disease from exposure to iAs.

Broberg *et al*. (2014) assessed the effects of arsenic on genome-wide DNA methylation in newborns in Matlab, Bangladesh. The study included 127 mothers and the cord blood from their infants. Arsenic exposure in early and late pregnancy was assessed by measuring concentration of arsenic metabolites in maternal urine. The median urinary arsenic concentration was 66 µg/L in gestation week (GW) 8 and 89 µg/L in GW 30. Maternal arsenic exposure in early gestation was associated with DNA methylation in the newborn child. For many of the sites, arsenic exposure was associated with a change in DNA methylation by several percentage points. The changes were observed at low levels, e.g., below 50 µg/L arsenic in the urine. The associations were more evident in boys than girls. Results suggested that arsenic affects accessible areas of the chromatin with certain structural features or impacts on specific transcription factors or other chromatin-associated proteins. Pathway analysis showed enrichment in DNA methylation changes in cancer-related genes in boys but not in girls. There were much stronger associations with arsenic exposure in early gestation compared to late gestation. Data also indicated a low capacity for methylation of arsenic with a higher fraction of MMA in the urine. How these observations relate to observed effects in early and late life needs to be elucidated.

Ahmed *et al*. (2013) studied children born into a longitudinal mother-child cohort in Bangladesh. Children were studied at 4.5 years (n=460) as well as birth (n=134). Exposure was assessed by urinary levels of iAs and its metabolites in both maternal and child urine samples. Associations with plasma concentrations of insulin-like growth factor 1 (IGF-1), calcium, vitamin D, intact parathyroid hormone, and phosphate were evaluated by linear regression analysis, adjusted for socioeconomic factors and child's sex. Prenatal arsenic exposure was inversely associated with plasma concentration of IGF-1 in neonates at birth. Arsenic exposure was associated with lower plasma concentrations of IGF-1 in preschool children. This effect was more evident in girls than in boys. IGF-1 is a mediator of the effects of growth hormone and is also a key regulator of the neonate immune response.

Ahmed *et al*. (2012) evaluated the effects of prenatal arsenic exposure on the function of the thymus, the primary site of T-cell lymphopoiesis during fetal life and early childhood. The fetal

thymus begins to produce T-cells prior to mid-gestation and this function is almost fully developed at birth. T-cells represent a subset of immune cells that play a key role in fighting infectious diseases and in promoting inflammation. Once a T-cell is activated, T cell effector functions can inhibit downstream events such as the synthesis of antibodies by B-cells. Therefore the prenatal period is likely to constitute a critical window for toxic insult on the immune system. In a Bangladesh cohort, arsenic was measured in urine at GW 8 and GW 30 and in the blood at GW 14 for 130 women. Child thymic index was measured by sonography at birth and thymic function by signal joint T-cell receptor rearrangement exclusion circles (TRECs) in cord blood monocytes. Maternal arsenic exposure during pregnancy was associated in a dose-dependent function with decreased TRECs levels in umbilical cord blood suggesting arsenic not only affected thymus size but also impaired the production of naïve T-cells, rendering infants more susceptible to infections. Reduced thymic function possibly resulted from induction of oxidative stress and apoptosis.

Prenatal arsenic exposure has been associated with reduced thymic index and increased morbidity in infants, indicating arsenic-related impaired immune function. Ahmed *et al*. (2014) studied the potential effects of pre- and post-natal exposure to iAs on cell-mediated immune function in pre-school age children. Children born in a prospective mother- child cohort in Matlab, a rural area of Bangladesh where there is an International Center for Diarrheal Disease Research, were followed up at 4.5 years of age (n=577) as part of an ongoing study concerning effects of arsenic on child health and development. Arsenic exposure was assessed by concentrations of arsenic metabolites in the urine of the children and mothers during pregnancy. For assessment of delayed-type hypersensitivity response, an intradermal injection of purified protein derivative was given to Bacillus Calmette-Guerin vaccinated children. Plasma concentrations of 27 cytokines were analyzed. Cytokines are proteins that are produced by cells. Cytokines interact with cells of the immune system in order to regulate the body's response to disease and infection. Cytokines also mediate normal cellular processes in the body. Associations were particularly strong in children with recent infections. Two cytokines (IL-2 and TNF-alpha) were associated with arsenic exposure. The researchers found significantly lower plasma IL-2 concentrations and non-significantly lower TNF-alpha levels in the highest arsenic exposed group (median= 232 µg/L) especially in children with recent infections. This is consistent with immunosuppression effects.

Luna *et al*. (2010) evaluated the effects of iAs, MMA, and DMA in a cross-sectional study performed in Zimapan, Hidalgo, Mexico. The source of drinking water was a deep aquifer. Arsenic concentrations ranged from 1-1054 µg/L (mean = approximately 580 µg/L). The study population was a random sample of 87 children, aged 6-10 years with no history of previous infectious disease during the two week prior to the study. Each child provided a blood and urine sample. The children had urinary arsenic levels ranging from 12.3 to 1411 µg/g creatinine. The study measured the differences in the levels of nitric oxide (NO) and superoxide anions in peripheral blood mononuclear cells and monocytes and NO and O^2 produced by activated

monocytes. There were statistical differences ($p<0.000$) among the groups. Positive association between urinary arsenic levels and venous levels of NO suggested the presence of incipient oxidative stress status in circulating blood cells from children exposed to arsenic.

Recent evidence suggested that arsenic carcinogenesis results from epigenetic changes, particularly DNA methylation. Intarasunanont *et al*. (2012) investigated DNA methylation changes as a result of arsenic exposure *in utero* and *in vitro*. A total of seventy- one newborns, were recruited from the southern peninsula of Thailand, of whom 55 were exposed to arsenic and 16 were unexposed. The mothers from both groups were matched for several relevant demographic characteristics e.g. socioeconomic and home environment. Arsenic exposure was measured in drinking water. Cord blood and newborn fingernails and toenails were sampled and used to assess exposure to arsenic. Arsenic-exposed newborns had significantly higher levels of arsenic in cord blood, fingernails, toenails and hair than unexposed. Cord blood lymphocytes were treated *in vitro* with arsenite at 1-100 uM for 2-8 hours and at 1.0 uM for eight weeks and results showed a slight increase in promoter methylation of p53 in cord blood lymphocyte which was then correlated with *in vivo* arsenic accumulation in nails ($p<0.05$). The study provided an important finding that *in utero* arsenic exposure affects DNA methylation, which may be linked to the mechanism of arsenic carcinogenesis through its key role in the control of gene expression. Data suggest that arsenic alters the immune system by influencing the CD4+/CD8+ T cell ratios, IL-2 cytokine levels and the expression of immune-response genes. Nadeau *et al*. (2014) investigated the impact of *in utero* environmental arsenic exposure on immune development and function in newborns participating in a pregnancy cohort in New Hampshire where arsenic levels exceeded the 10 µg/L EPA standard for drinking water. The study used a pregnancy cohort comprised of individuals spanning the dose-range of interest for arsenic water levels of 0 to 100 µg/L. Pregnant women were enrolled at 24-28 weeks of gestation. All pregnant women completed a self-administered lifestyle and medical history questionnaire. Researchers verified information about each participant's household water supply. Participants completed a diary of water, seafood, and rice intake for three days prior to urine collection. The study examined changes in immune cell profiles, T-cell functionality and gene expression measures. T-cell functions were analyzed for 16 cord blood samples from mothers with either the lowest or highest exposure to arsenic. Immune profiling was performed using cryopreserved lymphocytes from the first 116 of the remaining 129 pregnancies. Following delivery, placentas were biopsied adjacent to the cord insertion. To determine the effect of *in utero* arsenic exposure on neonatal immune function, cord T cell lymphocytes were phenotyped and identified by surface marker staining and flow cytometry. To assess functional capacity of T cells from neonates exposed to high levels of arsenic, researchers measured the ability of cord blood effector T cells to proliferate following *in vitro* TCR stimulation as well as the ability of cord blood regulatory T-cells (Tregs) to suppress the effector T cell function. Tregs are essential for the down regulation of T cell responses to both foreign and self-antigens and play an important role in several immune-mediated diseases, such as allergic diseases. Various studies have suggested that Tregs

may play a crucial role in early allergy protection by keeping the immune system in balance and counter-regulating potential default pathways. IL 1B is a marker of general inflammation and plays a direct and indirect role in T cell activation and differentiation. The study found that *in utero* arsenic exposure was related to a number of specific CD4+ T cell populations present in cord blood, increased cord blood T cell proliferation and greater IL 1B expression in the placenta. Results suggested the possibility that the effects previously seen in a higher-exposed pregnancy cohort from Bangladesh mirror what was seen in this population. Data suggested that specific immune-phenotypes of cord blood cells and impaired function of T cell subsets are associated with the extent of arsenic exposure prenatally. Relatively low level arsenic exposure *in utero* may alter the fetal immune system and lead to immune dysregulation.

Bailey *et al*. (2014) hypothesized that prenatal arsenic exposure is likely to perturb the expression levels of proteins in a variety of cellular processes in addition to the immune function. The objective of the research was to examine the proteomic shifts associated with prenatal iAs exposure using cord blood samples from 50 newborns in Gomez Palacio, Mexico. Levels of iAs and metabolites were determined in maternal urine along with levels in maternal drinking water in the range 0.456- 236 µg As/L. Cord blood samples representing a range of iAs exposures during prenatal periods (<1- 236 µg As/L) (25% > than 25 µg As/L) were analyzed for expression of proteins associated with maternal urine levels. A total of 111 proteins were identified for which there was a significant association between protein level in newborn cord blood and maternal urine total arsenic. Many of these proteins are regulated by tumor necrosis factor (TNF) and are enriched in functionality related to immune/inflammatory responses and cellular development/proliferation. Thirty were classified as “activators” because of a positive association between protein expression and maternal urine levels. Twenty were classified as “repressors” because newborns showed a negative association. The activator/repressor status was significantly associated with head circumference in male newborns, with activators having smaller head circumferences. This was not observed in female newborns. TNF has been predicted to regulate the fetal proteome.

Rahman *et al*. (2011) evaluated the association between arsenic exposure in pregnancy and morbidity during infancy. This prospective population cohort included 1552 live-born infants of women enrolled during 2002-2004 in Matlab, Bangladesh. Arsenic exposure was assessed by the concentrations of metabolites of inorganic arsenic in maternal urine samples collected at GW 8 and GW 30. Information on the symptoms of lower respiratory tract infections (LRTI) and diarrhea was collected by the 7-day recalls at monthly home visits. Approximately 115, 850 person-days of observations for infants were conducted in the 12 month follow-up period. The incidence of LRTI and severe LRTI was significantly higher in the highest quartile of exposure. Arsenic exposure was significantly associated with risk of lower respiratory tract infections and diarrhea in a dose-dependent manner. This study provides supporting evidence for the adverse impact of arsenic during the fetal period.

Farzan *et al*. (2013) recruited 18-45 year old pregnant women in the New Hampshire Birth Cohort Study. Each subject completed a medical history and lifestyle questionnaire. All subjects were private unregulated well water users. Each subject provided a urine sample at GW 24-28. A total of 214 mother-infant pairs were enrolled. The mean concentration of maternal total urinary arsenic was 3.7 µg/L with a range of 0.45-58.3 µg/L. At two weeks post-delivery, each subject completed another questionnaire regarding delivery outcomes and health of the infant. At four months after birth, subjects were contacted regarding the health status of their child, including any infections. Maternal arsenic levels during pregnancy were related to the number of infections found during subsequent annual evaluations for the first four years of a child's life. The data suggested that maternal As exposure during pregnancy may increase risk of infant infections early in life, including infections that require medical treatment. This study provided supporting evidence that early life respiratory infections increase the risk of later-childhood respiratory problems.

9.15.1.4 DISCUSSION

There is an emerging recognition of the importance of the epigenome in maintaining cellular homeostasis and that environmentally induced epigenetic perturbations may play an important role in disease development. The epigenome refers to potentially heritable biological information contained outside of the DNA sequence that functions as regulators of gene function. The environment of the developing child is an important determinant of disease susceptibility in adulthood, as this is a time of increased susceptibility to epigenetic changes (Gluckman, 2012; Duncan *et al.*, 2014).

Prenatal arsenic exposure has been associated with several epigenetic changes such as alterations in DNA methylation, which can alter developmental programming and gene expression, reduction in thymus size, effects on T-cells, and alterations in IGF-1, a key regulator of the neonate immune response, all indicating serious and irreversible effects on the developing immune system. Prenatal arsenic exposures are also associated with increased infant morbidity.

Molecular mechanisms underlying the adverse effects associated with arsenic are not well understood and are likely complex. It is plausible that several mechanisms are involved, possibly acting sequentially, simultaneously and/or synergistically. FDA will continue to monitor the literature, especially on research focusing on the modes of action of inorganic arsenic in the developing fetus and young children.

FDA conducted this literature search and analysis to determine if pivotal new data had emerged that would question or alter the conclusions of the qualitative assessment on inorganic arsenic's effects on the developing fetus or young child. The following questions were addressed by this review.

1) Are there new data that do not support the findings that inorganic arsenic is associated with adverse pregnancy outcomes?

   No. FDA identified additional studies that assessed the association of exposure to inorganic arsenic in utero with adverse pregnancy outcomes. These additional studies support our conclusion that exposure to inorganic arsenic during pregnancy is a concern to the developing fetus.

2) Are there new data that would enable FDA to calculate a point of departure for adverse pregnancy outcomes?

   No. The new data are not sufficient to develop a point of departure and/or reference dose for use in risk assessment. These papers do not provide adequate quantitative data upon which to calculate a point of departure. Some have very poor exposure data, or use very few subjects, or look at in vitro analysis of endpoints that cannot be easily quantitated with in vivo dosages. They also may present preliminary data which need to be confirmed by additional studies before it can be useful for quantitative analysis. The studies do however describe presumptive biomarkers of exposure and of effect which have the potential to identify adverse endpoints in larger, controlled studies.

3) Are there new data that do not support the findings that inorganic arsenic is associated with adverse neurodevelopmental effects in children?

   No. FDA identified additional studies that assessed the association of exposure to inorganic arsenic with neurobehavioral deficits. These additional studies support our conclusion that exposure to inorganic arsenic either in utero or in early childhood has adverse effects on neurobehavioral development.

4) Are there new data that would enable FDA to calculate a point of departure/reference dose for adverse neurodevelopmental effects on children?

   No. The new data are not sufficient to develop a point of departure and/or reference dose for use in risk assessment.

5) Are there any other non-cancer endpoints of significance that are emerging in the literature for the susceptible populations of pregnant women and infants and children?

   Yes. FDA identified several studies that demonstrate that iAs can act as an immunomodulatory agent in utero which may play a role in the development of the diverse adverse health effects associated with inorganic arsenic. These effects may be long-lasting.

While the data clearly indicate that inorganic arsenic can have a detrimental effect on the developing immune system, there are not sufficient data to determine at what exposures these impacts might occur.

9.15.2 AN UPDATE OF THE LITERATURE ON ADVERSE EFFECTS OF INORGANIC ARSENIC EXPOSURE ON CANCER ENDPOINTS IN ALL EXPOSED POPULATIONS

With respect to the cancer endpoints, we conducted a literature search and analysis to address the following questions:

1) Are there new data that would enable FDA to refine its dose-response cancer estimations for exposure to inorganic arsenic?

2) Are there new data that support the use of a different and/or additional cancer endpoints?

3) Are there new data in the literature that would impact on the conclusions for the cancer endpoints discussed in the RA?

At the request of the FDA, Oak Ridge National Library conducted a search of the literature from October 2013 to February 2014. The following search strategy was employed: Search: (arsenic AND carcinogen(s) and arsenic AND neoplasm(s).

Search results, including abstracts, were provided to FDA from the National Center for Biotechnology Information at the U.S. National Library of Medicine. Over one hundred and forty papers were initially identified. For research papers to be included in this analysis, the criteria used in the RA were also applied here:

- Review focused on the effects of inorganic arsenic exposure by the oral route

- Review considered the health effects reported in epidemiology studies regardless of the country of origin

Below is a synopsis of the pertinent new papers identified. The papers were sorted into five main topics- Lung Cancer, Bladder Cancer, Skin Cancer, Other Cancers, and Cancer Mortality.

9.15.2.1 LUNG CANCER

As and Lung Cancer Latency and Lung Cancer at Low As Exposures

The latency period for arsenic-induced disease is long and has recently been investigated by researchers. Steinmaus *et al*. (2013) conducted a population-based case-control study evaluating As water concentration and lung cancer risk in Northern Chile. The population of focus was inadvertently exposed to high As in drinking water for 12 years and then lung cancer risk evaluated 40 years after high exposure ceased. Lung cancer odds ratios (OR) corresponding to arsenic concentrations in drinking water of < 11 µg/L, 11-90 µg/L, 91-335 µg/L and > 335 µg/L were 1.0, 1.27 (95% confidence interval [CI]: 0.81-1.98), 2.0 (95% CI: 1.24-3.24) and 4.32 (95%CI: 2.6-7.17). These data suggest high risk of lung cancer 40 years post high As drinking water exposure.

While As concentration in water > 400 µg/L has generally been associated with increased risk for lung cancer, the risk of cancer at lower As exposures (< 100-200 µg/L) continues to be debated (see Lamm *et al*. (2014) and Lamm *et al*. (2015b)). The low increased risk at these lower exposure levels is not likely to be observed with the actual available data due to difficulty obtaining long-term exposure data and statistical power. Steinmaus *et al*. (2014)[3] assessed As-induced cancer latency 40 years post-exposure but in low exposure populations (< 100 µg/L As in water) within Northern Chile. The adjusted ORs were 1.0, 1.43 (90%CI: 0.82-2.52) and 2.01 (90%CI: 1.14-3.52) for mean As water concentrations of 6.5, 23 and 58.6 µg/L, respectively. When only subjects <65 years old were considered, ORs increased. Additionally, Dauphine *et al*. (2013) evaluated As-induced cancer latency in a US population. They compared 196 lung cancer patients to 359 age-, gender-, location (CA, NV)-matched controls for As concentration in water and risk of lung cancer 40 years after exposure. The lung cancer OR in people who consumed water containing a 5 year average As concentration of > 85 µg/L was 1.39 (95%CI: 0.55-3.53) and, in smokers 1.61 (95%CI: 0.59-4.38). Given the large CIs, these data suggested that large sample sizes are usually needed to establish As-related health effects at low exposures.

Genetic and Environmental Factors Potentially Contributing to As-associated Lung Cancer

Many genetic and environmental factors likely contribute to the risk of developing lung cancer from arsenic exposure. One genetic factor that may play a role is the capacity to metabolize inorganic arsenic. Humans primarily metabolize inorganic arsenic by first methylating it to MMA, then to DMA and then excreting via urine. People less efficient in metabolizing As via methylation may have greater urinary MMA and be more prone to As-related cancer.

Melak *et al*. (2014) related urinary As metabolites to lung cancer odds ratios (ORs) in a population from northern Chile exposed to As via drinking water. Increasing tertiles of % urinary MMA (MMA3 and MMA5) yielded adjusted (age, sex smoking) ORs of 1.0, 1.91 (95%CI: 0.99-

[3] In papers published after the completion of this risk assessment, the Steinmaus *et al*. (2014) finding of increased lung cancer in an examination of persons with 40 years post-exposure to arsenic for water concentration under 1000 µg/L was subject to criticism from two authors (see Lamm *et al*. (2015a) and Slim and Sewitch (2015)).

3.67) and 3.26 (95% CI:1.76-6.04) for lung cancer (trend: $p < 0.001$). After adjusting for As water concentrations, the OR comparing the upper tertile of % MMA to the lower exposure ranges for lung cancer was 2.32 (95% CI: 1.40-3.87). These data suggest As methylation capacity might contribute to As-related lung cancer. However, the lung cancer OR also depended on the As concentration in water. For those in the upper tertile of % urinary MMA, the lung cancer OR was 2.48 for those with As water concentrations < 200 µg/L while the OR was 6.81 for those with As water concentrations > 200 µg/L.

Environmental factors such as smoking status or occupational exposure were shown to contribute to As-induced lung cancer risk. For example, Khlifi *et al.* (2014) demonstrated that laryngeal and nasopharyngeal cancer risk was significantly associated with high blood levels of As and cadmium with OR equal to 2.41 and 4.95, respectively, upon controlling for tobacco smoking, tobacco chewing and alcohol consumption. However, within this study, tobacco smoking and chewing and occupational exposure to these metals was significantly associated with these cancers (OR = 10.22 and 10.38, respectively, $p < 0.001$).

Ferreccio *et al.* (2013b) evaluated the effects of smoking status and lifetime arsenic exposure via water on lung cancer incidence in Northern Chile. The OR for low As exposure (<11 µg/L water) and lung cancer in never smokers was 1.0, while for smokers it was 3.8 (95% CI 1.7-8.5). The OR for high As exposure (> 335 µg/L water) and lung cancer in never smokers was 2.0 (95% CI 0.8-5.0), while for smokers it was 16 (95% CI 6.5-40). Greater than additive effects for As and smoking (tobacco) were observed for people exposed to > 335 µg/L As in water. This trend was seen in people coexposed to As and secondhand smoke as well. In patients who smoke and have lung cancer, blood and hair As concentrations were significantly greater ($p < 0.001$) than in location- matched controls (Wadhwa *et al.*, 2013) without lung cancer suggesting As water concentration wasn't solely responsible for lung cancer incidence. While smoking might synergistically increase lung cancer risk from As exposure, levels of arsenic in lung tumors were not associated with smoking status, histopathological tumor type and TNM staging (Demir *et al*., 2014).

9.15.2.2 BLADDER CANCER

As and Bladder Cancer Latency and Bladder Cancer at Low As Exposures

Steinmaus *et al*. (2013) conducted a population-based case-control study evaluating As water concentration and bladder cancer risk in Northern Chile. The population of focus was exposed to high As in drinking water for 13 years (1958-1970) and then bladder cancer risk evaluated 40 years after high exposure ceased. Bladder cancer ORs corresponding to average As concentrations in drinking water of < 11 µg/L, 11-90 µg/L, 91-335 µg/L and > 335 µg/L were 1.0, 1.36 (95% CI: 0.78-2.37), 3.87 (95% CI: 2.25-6.64) and 6.50 (95% CI: 3.69-11.43).

Fernandez *et al*. (2012) evaluated a subset of the Northern Chile population, focusing only on Antofagasta and bladder cancer mortality, rather than incidence. From approximately 1955-1980, people in Antofagasta, Northern Chile were exposed to As in drinking water > 100 µg/L, sometimes reaching concentrations of >500-600 µg/L. Data showed an increased mortality rate risk of 5.3 (95% CI: 4.8-5.8) for men and 7.8 (95% CI: 7.0-8.7) for women between 1983-2009 compared to the rest of the country. Furthermore, compared to the general population, mean age at bladder cancer specific death was significantly lower in the Antofagasta population. Taken together, these data suggest high As exposure increased bladder cancer mortality risk and decreased age of mortality due to bladder cancer, two significant outcomes that were delayed decades after high As exposure occurred.

While the carcinogenic effects of high inorganic As exposure are well documented, the cancer risk at low As exposures are still being investigated. In 2013, a review of epidemiological evidence (2000-2013; 20 epidemiologic studies identified) revealed that most studies demonstrated that As exposure significantly increased bladder cancer risk at > 50 µg/L As water concentration but also concluded that associating As exposure with bladder cancer in lower exposure paradigms would require more data. Later, Tsuji *et al*. (2014) performed a meta-analysis to examine bladder cancer risk at low-level As exposure. For the 9 studies included, the summary relative risk estimate (SSRE) of bladder cancer from low As exposure (e.g. < 100 – 200 µg/L) was not significant (SSRE=1.07; 95% CI: 0.95-1.21). The overall conclusion was similar when stratifying by smoking status (never *vs*. ever), except for ever smokers within the cumulative exposure metric (SSRE=2.35; 95% CI:1.51-3.66) and for studies performed in the United States. Lamm and researchers examined the cancer (lung and bladder combined) risk (cancer slope factor) associated with low As exposures in 18 villages of southwest Taiwan where As well water concentrations were known (Lamm *et al.*, 2013). Using a Poisson Analysis, researchers related median (As well water concentration < 150 µg/µL), mean (excluding 3 villages with As well water concentrations > 500 µg/dL) and maximum (excludes 4 villages where any well water As level > 150 µg/L) As well water concentrations to cancer risk. In all three scenarios the cancer slope factor was negative. This pattern could be attributed to data selection and not including the population of southwest Taiwan as a village with As well water concentration of 0 µg/L. In a similar analysis, Lamm *et al.* (2014) related cancer (lung and bladder combined) risk (cancer slope factor) to low and high As exposures in 42 villages from southwest Taiwan with known As well water concentrations. Median, mean and maximum well water concentrations were modeled using a backward stepwise sequential reductive Poisson analysis, which calculated cancer slope factors upon removal of the 4 villages with the highest exposure. Overall results showed a positive cancer slope factor above 200 µg/L As and a negative cancer slope factor below 150 µg/L with statistical significance at various concentrations depending on the exposure metric.

Genetic and Environmental Factors Potentially Contributing to As-associated Bladder Cancer

In addition to high As exposure, tobacco smoke exposure is one environmental factor known to increase risk of bladder cancer. Wu *et al*. (2013) investigated the joint effects of cigarette smoking, exposure to secondhand smoke and total urinary As levels on urothelial cancer (UC) risk. In patients with low urinary As (< 15.40 µg/g creatinine), cigarette smoking and secondhand cigarette exposure increased the OR for UC. This trend was also seen for cases of high urinary As (≥15.40 µg/g) with ORs of 3.06 (95% CI: 1.55–6.01), 5.55 (95% CI: 2.72–11.30), 5.55 (95% CI: 2.67–11.54), and 10.82 (95% CI: 5.16–22.69) for those who are not exposed to cigarette smoke, are exposed to only secondhand smoke, are cigarette smokers, and are cigarette smokers and exposed to cigarette smoke, respectively, relative to no smoke exposure low urinary total As controls.

Ferreccio *et al*. (2013b) evaluated the joint effects of smoking status and lifetime arsenic exposure on bladder and lung cancer incidence in Northern Chile. The odds ratios (OR) for low As exposure (< 11 µg/L water) and bladder cancer in never smokers was 1.0, while for smokers it was 4.1 (95% CI: 1.3–13). OR for high As exposure (> 335 µg/L water) and bladder cancer in never smokers was 8.9 (95% CI: 3.0–26), while for high-exposure smokers it was 23 (95% CI: 8.2–66). Synergistic effects of smoking and arsenic on bladder cancer risk was observed with a Rothman Synergy Index of 2.0 (95% CI: 0.92–4.5) and a Synergy index for secondhand smoking and arsenic on bladder cancer of 2.6. These data suggest bladder cancer risk from As and tobacco smoke exposure combined could be greater than summing the bladder cancer risk from each exposure individually.

As noted earlier in this document, the capacity of an individual to metabolize As is one genetic factor that could increase risk of developing cancer from As exposure. People less efficient in metabolizing As via methylation may have greater urinary iAs and MMA and therefore, be more prone to As-related cancer. Melak *et al*. (2014) related urinary As metabolites to bladder cancer OR in a population from Northern Chile exposed to As via drinking water. Increasing tertiles of % urinary MMA yielded adjusted ORs of 1.0, 1.81 (95 %CI: 1.06–3.11) and 2.02 (95% CI: 1.15–3.54) for bladder cancer (trend: $p < 0.001$). After adjusting for As water concentrations, the OR comparing the upper tertile of % MMA to the lower two for bladder cancer was 1.53 (95 % CI: 0.94–2.49).

Because data suggest the capacity to methylate MMA to DMA might contribute to As-related bladder cancer, Beebe-Dimmer *et al*. (2012) evaluated the relationship between bladder cancer and single nucleotide polymorphisms (SNPs) in 3 genes related to As-metabolism, Glutathione-S-Transferase Omega-1 (GSTO-1), Methylene-tetrahydrofolate Reductase (MTHFR) and Arsenic (+3) Methyltransferase (As3MT). Within genotypes there were significant interactions with SNPs of As3MT and higher average As exposure, particularly that 1+ copies of C allele rs11191439 was associated with increased bladder cancer risk (OR = 1.17, 95% CI: 1.01–1.32 for every 1 µg/L increase in As water concentration). As3MT haplotype was associated with

bladder cancer risk in participants exposed to As in the greatest quartile of exposure (> 3.72 µg/L As water concentration). The authors concluded that while these results suggest SNPs in As3MT and As exposure are associated with an increased risk for development of bladder cancer, it is difficult to attribute these findings to one SNP because of linkage disequilibrium.

Yang *et al*. (2014) compared genome-wide deoxyribonucleic acid (DNA) methylation profiles of urothelial carcinoma tissue in patients with As induced UC (patients had been living in the arseniasis-endemic areas of southwestern Taiwan for > 10 years) and of patients with non-As induced UC (never lived in arseniasis-endemic areas). Methylation level of 5 genes were significantly associated to cumulative As exposure in smoking-unrelated UC. The cellular functions of the hypermethylated genes identified were cell adhesion, proteolysis, ion transport, transcriptional regulation and neuronal signaling.

9.15.2.3 SKIN CANCER

Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are two types of non-melanoma skin cancer (NMSC) potentially associated with As exposure. From a case-control study population in New Hampshire, Gilbert-Diamond *et al*. (2013) related squamous cell carcinoma (SCC) to urinary arsenic metabolites and to concentrations of As in private well water commonly found in the United States. For every µg/L increase in ln-transformed As water concentration, the OR for SCC was 1.37 (95% CI: 1.04–1.80). Similar patterns were observed for SCC and urinary ln(MMA), ln(DMA) and ln(iAs).

Leonardi *et al*. (2012) associated basal cell carcinoma (BCC) with lifetime As drinking water concentrations (< 100 µg/L As) and urinary As metabolites in a multi-national European population. Analyses demonstrated a dose-dependent increase in OR of BCC with increasing lifetime As water concentrations. The OR for BCC in the top two quintiles of exposure were 1.73 (95% CI: 0.97–3.11) and 3.03 (95% CI: 1.7–5.41). Lower % urinary DMA and higher % urinary MMA were associated with increased BCC risk.

In the same multi-national European population described above, Surdu *et al*. (2014) related polymorphisms in the DNA repair genes XRCC1 and XRCC3 with NMSC risk and As and sunlight exposure. Patients with the AA variant of XRCCI R399Q exhibited significantly increased OR for NMSC. However, authors observed no significant combined effects on NMSC OR with this genotype, sunlight and As exposure. The study suggests an interaction between the effect of XRCC3 T241M polymorphism and the effect of work-related sunlight exposure on NMSC risk ($p < 0.10$) and an interaction between the effect of XRCC3 T241M polymorphism and drinking water As exposure on NMSC risk ($p < 0.10$). Within specific XRCC3 T241M genotypes, As exposure through drinking water modified NMSC risk. Taken together, these 3 studies demonstrate a relationship between As exposure and NMSC risk and show capacity of genetic factors to modify cancer risk when patients are exposed to As and sunlight.

9.15.2.4 OTHER CANCERS

Kidney: A case-control study was conducted in Chile that included 122 cases for 640 population based controls to evaluate the association of kidney cancer and iAs (Ferreccio *et al.*, 2013a). Cases included 76 renal cell, 24 transitional cell renal pelvis and ureter, and 22 other kidney cancers. For renal pelvis and ureter cancers, the adjusted odds ratios by average arsenic intakes of < 400, 400 to 1,000, and > 1,000 µg/day (median water concentrations of 60, 300, and 860 µg/L) were 1.00, 5.71 (95% CI: 1.65, 19.82), and 11.09 (95% CI: 3.60, 34.16) (trend: $p < 0.001$), respectively. Odds ratios were not elevated for renal cell cancer. In rural Bangladesh, Mostafa and Cherry (2013), found a significant relationship between the arsenic concentration in well water and both renal cell cancers and transitional cell cancers. While these studies suggest an association between renal cancer and As exposure, renal cancer was not a main focus in this risk assessment and therefore, no dose-response model developed.

Liver: In a retrospective, ecological analysis performed in Taiwan, Lin *et al*. (2013) compared arsenic levels in drinking water with liver cancer as verified in a review of death certificates from 1971 to 1990. The authors concluded that exposures to high arsenic levels in drinking water (0.64 mg/L) are significantly associated with the occurrence of liver cancer. While the association of long-term iAs exposure through drinking water with risk of liver cancer mortality was controversial, Wang *et al*. (2014) concluded in a meta-analysis that drinking water increases the risk of liver cancer mortality. The data are nevertheless insufficient to derive a complete dose-response model for liver cancer.

Others cancers: While more research is available on iAs exposure and the risk of other cancers, e.g., leukemia (Heck *et al.*, 2014), breast cancer (Lopez-Carrillo *et al.*, 2014), scrotal carcinoma (Koc *et al.*, 2014) and stomach cancer (Kreuzer *et al.*, 2012), insufficient data are currently available to quantitatively estimate the corresponding risks.

9.15.2.5 DISCUSSION

FDA conducted this literature search and analysis to determine if pivotal new data had emerged that would question or alter the conclusions of the RA. The following questions were addressed by this review.

1) Are there new data that would enable FDA to refine its dose-response cancer estimations for exposure to inorganic arsenic?

   No. New data have provided additional evidence that exposure at early life-stages may have a greater impact on the development of certain arsenic-related cancers. This was also emphasized by the NRC Report on Inorganic Arsenic. The question of how to model

for this effect has still not been resolved. FDA has discussed this issue with the EPA and will be one of the questions asked when the RA is peer-reviewed.

2) Are there new data that support the use of different and/or additional cancer endpoints as part of its evaluation of the carcinogenic?

   No. Although literature is emerging on several additional cancers associated with arsenic exposure, there are not enough data on these tumors to use in a quantitative risk assessment.

3) Are there new data in the literature that would impact on the conclusions for the cancer endpoints discussed in the RA?

   No. The new literature describes possible modes of action for carcinogenic effects of arsenic as well as several potential biomarkers. These data support our concerns for the carcinogenic effects of inorganic arsenic as a carcinogen but are not rigorous enough to justify modifying our quantitative risk assessment.

9.15.3 CONCLUSIONS

We determined that the new literature published after we completed our risk assessment supports the findings in our risk assessment. A large amount of literature has been published on possible modes of action for inorganic arsenic and several promising biomarkers for arsenic exposure and effects have been described. However, none of this research is sufficiently developed to be useful in quantitative risk assessment. Since these are all areas of considerable research, the FDA Arsenic Risk Assessment Team will continue to monitor closely the emerging literature.