External Peer Review Report

Arsenic in Rice and Rice Products Risk Assessment: Draft Report, Addendum, and Model

December 4, 2015

Versar Contract No. HHSF223201210011B

Contents

I. INTRODUCTION

As part of FDA's ongoing effort to identify the risk associated with exposure to inorganic arsenic in rice and rice products, FDA conducted a risk assessment concerning health risks associated with consumption of inorganic arsenic in rice and rice products. The purpose of this assessment was to examine available scientific data and information to provide quantitative estimates of cancer risk presented by long-term exposure from inorganic arsenic in rice and rice products. In addition, the risk assessment qualitatively addressed the possible non-cancer health effects from pre- and post-natal exposure to inorganic arsenic in rice and rice products. This examination of the current science and predictive model are among the tools that FDA will use to evaluate current and potential new policies, programs and mandatory or voluntary practices to minimize the public health impact of this and other naturally occurring contaminants in the food supply. This work provides a comprehensive assessment that builds on and improves upon previously conducted FDA assessments and evaluations, and incorporates new information, where applicable. Versar, Inc., managed the peer review process including selecting the five peer review experts who independently reviewed the documents and model, and provided written comments.

Peer Reviewers:

Aaron Barchowsky, Ph.D.
Department of Environmental and Occupational Health, Graduate School of Public Health
University of Pittsburgh
Pittsburgh, PA 15219

Rebecca C. Fry, Ph.D.
Michael Hooker Research Center
Chapel Hill, NC 27599

Barry P. Rosen, Ph.D.
Herbert Wertheim College of Medicine
Florida International University
Miami, FL 33199

Craig M. Steinmaus, M.D., M.P.H.
Director, Arsenic Health Effects Research Group
University of California, Berkeley
Oakland, CA 94612

Marie Vahter, Ph.D.
Institute of Environmental Medicine
Karolinska Institutet
Stockholm, Sweden

II. CHARGE TO REVIEWERS

Charge Questions:

1. The risk assessment focuses on the risk associated with consumption of rice and rice products.
   1.1. Have we adequately explained why FDA focused on these foods?
   1.2. If not, what additional information should we provide?

2. Although we did not conduct a comprehensive literature search of all publications on all aspects of arsenic, we relied upon and cited other sources that have extensively reviewed the literature. Additionally, we included the newer research being published, especially on susceptible populations. With this in mind, did we include all pertinent recent literature?

3. Do you agree with the dose-response modeling approach, data selected, and assumptions that we used for assessing the lung and bladder cancer risk estimates?
   3.1. If not, what alternative modeling approaches should we consider? Specifically we are interested in comments on the model weighting used. For example, how much weight should be given to the different alternative models and what is your scientific rationale for the choices?
      3.1.1. Additionally please comment on whether our use of the Morales model is consistent with the way it was used in developing the EPA 2001 Drinking Water Rule.
   3.2. Given the challenges of using epidemiology data for dose-response modeling and especially in this case, using data from non-U.S. population, please comment on whether FDA adequately justified the selected studies (Chen *et al.*). If not, what additional information should we provide in the report?

4. For prenatal and early life exposure, are there enough data of sufficient quality to develop a dose-response model and quantify the risk estimate for these two exposure periods (life stages)? If not, do you have suggestions to strengthen the text and to assist in the estimation of risk for adverse pregnancy and developmental outcomes?

5. Do you agree with our approach to exposure assessment, including the data and assumptions used. If not, what alternative approaches, data or assumptions should we consider?

6. Do you agree with the assumptions and scenarios we presented in the "What if?" section of the risk characterization? Are there other scenarios that should be included?
   6.1. If so, please explain why and provide details about the additional scenarios for FDA to consider.

7. Do you think the key findings and conclusions that we made are supported by the information provided in the risk assessment? If not, please explain what alternative findings and conclusions should be considered.

8. Do you have any other comments or suggestions that are not elicited by 1-7?

III. INDIVIDUAL REVIEWER COMMENTS

I. Reviewer # 1

Peer Review Comments on Arsenic in Rice and Rice Products Risk Assessment:

Draft Report, Addendum, and Model

Reviewer #1

I. GENERAL IMPRESSIONS

My overall impression is that the FDA is justified to be concerned about the levels of arsenic in rice and rice products.

My first impression was that the increased risk of cancer with arsenic in food is significant. But, upon further reading, I asked if the increase in cancer risk justifies new regulations on arsenic in rice. The added number of cases that is estimated to be attributable to arsenic is 39/million (0.0039%) compared with 90,000/million (9%) from all causes. Should this very tiny increase be of concern to the FDA? (See p. 13: "*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). 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*," p. 17: "*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);*" and p. 18: "*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).* From the what-if calculations, rice would need to be reduced to less than 75 ppb to have a significant effect on the cancer risk, and this would wipe out the U.S. rice market.

However, cancer risk is not the only factor. Although the current overall risk does not appear to increase the probable lifetime incidence of lung and kidney cancer in the general population, the likely epigenetic and neurological and development effects on pregnant women, fetuses, infants and children make it imperative to gather more data on the qualitative aspects of exposure.

II. RESPONSE TO CHARGE QUESTIONS

1. The risk assessment focuses on the risk associated with consumption of rice and rice products.

1.1. Have we adequately explained why FDA focused on these foods?

The presentation of the documents was quite clear. The justification for limiting the risk analysis to only inorganic arsenic and primarily white rice is reasonable. The amounts and toxicity of organic arsenic are too low to add significant risk. Rice is the primary source of arsenic in the diet after seafood, where the arsenic is primarily nontoxic organic species. It is not clear if hyperaccumulation in rice is from genetic factors such as increased numbers or expression of

aquaglyceroporins or because rice can be grown in flooded conditions, where more of the arsenic is reduced and mobile, or a combination of the two.

1.2. If not, what additional information should we provide?

[The reviewer did not comment.]

2. Although we did not conduct a comprehensive literature search of all publications on all aspects of arsenic, we relied upon and cited other sources that have extensively reviewed the literature. Additionally, we included the newer research being published, especially on susceptible populations. With this in mind, did we include all pertinent recent literature?

The literature search was quite comprehensive. There are a few new publications that could be considered.
1. Dheeman DS, Packianathan C, Pillai JK, Rosen BP. 2014. Pathway of human AS3MT arsenic methylation. *Chemical Research in Toxicology*, 27:1979-1989. In this study from my own laboratory on the mechanism of human AS3MT, we propose a new and distinctive pathway for methylation that is different from that of either Challenger or Hirano but includes aspects of both and should be considered a successor to both. The important conclusion is that the products are the toxic and carcinogenic trivalent methylated species, and not the relatively nontoxic pentavalent species.

2. My recent review article (Zhu, Y.G., Yoshinaga, M., Zhao, F. and Rosen, B.P. Earth abides arsenic biotransformations, *Ann. Rev. Earth and Planetary Sci.*, 42:443–467 (2014)) might provide useful background information.

3. There is a series of recent publications by Ana Navas-Acien of Johns Hopkins University School of Public Health on the Strong Heart Study, a population-based prospective cohort study of the health consequences of arsenic exposure in American Indians in Arizona, Oklahoma and North and South Dakota. Arsenic exposure was related to increased cardiovascular disease, type 2 diabetes, and cancer.

- Weidemann D, Kuo CC, Navas-Acien A, Abraham AG, Weaver V, Fadrowski J. Association of arsenic with kidney function in adolescents and young adults: Results from the National Health and Nutrition Examination Survey 2009-2012. E*nviron Res.*, 140:317-324 (2015).
- Kuo CC, Howard BV, Umans JG, Gribble MO, Best LG, Francesconi KA, Goessler W, Lee E, Guallar E, Navas-Acien A. Arsenic exposure, arsenic metabolism, and incident diabetes in the strong heart study. *Diabetes Care*, 38:620-627 (2015).
- Zheng LY, Umans JG, Tellez-Plaza M, Yeh F, Francesconi KA, Goessler W, Silbergeld EK, Guallar E, Howard BV, Weaver VM, Navas-Acien A. Urine arsenic and prevalent albuminuria: evidence from a population-based study. *Am J. Kidney Dis.*, 61:385-394 (2012).
- Gribble MO, Howard BV, Umans JG, Shara NM, Francesconi KA, Goessler W, Crainiceanu CM, Silbergeld EK, Guallar E, Navas-Acien A. Arsenic exposure, diabetes prevalence, and diabetes control in the Strong Heart Study. *Am. J. Epidemiol.*, 176:865-874 (2012).

4. Schlebusch CM, Lewis CM, Jr., Vahter M, Engstrom K, Tito RY, Obregon-Tito AJ, Huerta D,

Polo SI, Medina AC, Brutsaert TD, Concha G, Jakobsson M, Broberg K. 2013. Possible positive selection for an arsenic-protective haplotype in humans. *Environ Health Perspect.*, 121:53-58. In this very interesting paper, Schlebusch and coworkers demonstrated that long-term high-level arsenic exposure can select for arsenic-protective AS3MT haplotypes. It is not clear how this could be applicable to current U.S. exposures, but it might affect how data from long-term studies of populations in high-level exposure are used if individuals in those populations develop fewer arsenic-related diseases than predicted.

3. Do you agree with the dose-response modeling approach, data selected, and assumptions that we used for assessing the lung and bladder cancer risk estimates? If not, what alternative modeling approaches should we consider? Specifically we are interested in comments on the model weighting used. For example, how much weight should be given to the different alternative models and what is your scientific rationale for the choices?

In general, I agree with the dose-response modeling approach. The Taiwanese studies are the only well-documented long-term data. I do have a few concerns about the basis for the model. In both Chen 2010a and Chen 2010b, the increased risk of either lung or urinary tract cancer between 10 and 100 ppm is not statistically significant. Chen *et al.* (2010b) suggested on p. 459 that there may be a threshold, which is not consistent with the Morales linear model. Since these studies are the basis for the current model, a possible threshold should be considered.

In addition, the model based on the Chen studies considers only arsenic in drinking water and not in rice. However, ingestion of arsenic in rice is in addition to arsenic in drinking water, so the risk may be additive. In Taiwan rice is the major staple, and, according to Meharg, Taiwanese rice contains substantial amounts of arsenic. I am not sure whether either the Chen 2010a or Chen 2010b studies took food sources of arsenic into account.

3.1. If not, what alternative modeling approaches should we consider? Specifically we are interested in comments on the model weighting used. For example, how much weight should be given to the different alternative models and what is your scientific rationale for the choices?

I have no comments on the weighting.

3.1.1. Additionally please comment on whether our use of the Morales model is consistent with the way it was used in developing the EPA 2001 Drinking Water Rule.

Overall, the Morales model should be useful for FDA decision-making. However, as mentioned above, the Chen *et al.* (2010b) publication suggested that there might a threshold at arsenic concentrations below 50 ppm.

3.2. Given the challenges of using epidemiology data for dose-response modeling and especially in this case, using data from non-U.S. population, please comment on whether FDA adequately justified the selected studies (Chen et al.). If not, what additional information should we provide in the report?

Inclusion of studies on Taiwanese populations is justified primarily because there are no comparable data on U.S. populations. The Strong Heart Study might be considered, but it does

not have the same length of data collection as the Chen studies, and it is restricted to a single ethnic U.S. population (Native Americans). It might be useful as a supplement to but not as a replacement for the Chen studies.
I have two other concerns about data. First, I am not aware if either the Chen 2010a or Chen 2010b studies considered food sources of arsenic. Rice is a major food source for the Taiwanese population. Taiwanese rice has high levels of arsenic, and the rice consumed by people in high-arsenic regions of Taiwan may have more arsenic than the average. Thus, total arsenic exposure may be higher than reported in the Chen studies.

Second, this may seem far-fetched, but is it possible that the Taiwanese populations have adapted to the high levels of arsenic and develop few cancers as a result? Recently Schlebusch and coworkers demonstrated that populations in high-arsenic regions have arsenic-protective AS3MT haplotypes (Schlebusch CM, Lewis CM, Jr., Vahter M, Engstrom K, Tito RY, Obregon-Tito AJ, Huerta D, Polo SI, Medina AC, Brutsaert TD, Concha G, Jakobsson M, Broberg K. 2013. Possible positive selection for an arsenic-protective haplotype in humans. Environ Health Perspect 121:53-58.). The Chen studies do not take into account the possibility that Taiwanese populations exposed to high levels of arsenic in drinking water for generations may have adapted as the Andean populations have. If there has been any adaptation, then the observed increased risk in Taiwanese populations may be skewed toward lower values, that is, more urinary tract or lung cancers would be expected for non-adapted populations. This cannot be discounted since the occurrence of AS3MT haplotypes has not been examined in Taiwanese populations.

4. For prenatal and early life exposure, are there enough data of sufficient quality to develop a dose-response model and quantify the risk estimate for these two exposure periods (life stages)? If not, do you have suggestions to strengthen the text and to assist in the estimation of risk for adverse pregnancy and developmental outcomes?

While there are insufficient data to develop a quantitative model for these life stages, there are sufficient qualitative data to warrant restricting exposure now. I would suggest putting more emphasis in the report on the effects of low level arsenic exposure to fetuses, infants and children and less emphasis on studies of cancer risk with high levels of arsenic in drinking water not found in the U.S.

5. Do you agree with our approach to exposure assessment, including the data and assumptions used. If not, what alternative approaches, data or assumptions should we consider?

For the most part, I agree with the approach, data and assumptions. However, the assumptions are based on consumption by the current overall U.S. population (p. 3: *The average American diet includes less than one serving of rice and rice products per day;"* and from p. 49: Section 4.3.1 CONSUMPTION DATA). This assumption does not take into account the differences in rice consumption in ethnic populations and the changing population of the United States. On p. 55 is the statement "*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*."

My concern is that only present day consumption is considered. Members of ethnic populations such as Asian and Hispanics consume considerably more rice on a daily basis than the present majority population in this country (p. 55, Fig. 4.5). The what-if on p. 83 (Table 5.9) considers different consumptions. March 2015 projections by the U.S. Census Bureau estimate that the percentage of the Asian population in the U.S. will increase from 5.4% in 2014 to 9.3% in 2060, and that the Hispanic population will increase from 17.4% in 2014 to 28.6% in 2060. Thus these two populations comprise about 23% of the total population in 2014 and will increase to nearly half the U.S. population by 2060. Assuming that these populations continue to consume rice at their present levels, exposure to arsenic and rice products will increase dramatically in the following decades, along with the risk of arsenic-related health effects. This is not just a what-if; it is a near certainty.

6. Do you agree with the assumptions and scenarios we presented in the "What if?" section of the risk characterization?

I think that the what-if for limiting arsenic in infant diets would have the most dramatic effect on risk, especially the 4-fold decrease in risk by limiting arsenic in rice and rice products from ages 0-6. It might temporarily impact the baby food market, but market forces will compel the companies to develop alternative baby foods. In contrast, there is not much effect on cancer risk of limiting arsenic in rice to 200 ppb (p. 78, Table 5.6). To make a meaningful impact on risk, the limit would have to be less than 75 ppm, which might result in a loss of nearly the entire U.S. rice market.

6.1. Are there other scenarios that should be included? If so, please explain why and provide details about the additional scenarios for FDA to consider.

The additive risk of arsenic in water with arsenic in rice should be considered. There seems to be some discontinuity between considerations of the risk of arsenic in drinking water and the risk of arsenic in rice. Both sources of arsenic contribute to risk, but they appear to be considered separately. The drinking water studies do not appear to take food arsenic into account, and the food studies don't seem to count the amount of arsenic in water. For example, on p. 22 is the statement, "*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 at the individual level."*

Thus, the effects of arsenic in rice, the contribution from the arsenic in drinking water, and the arsenic in the water used to cook rice should be added to the amount from the rice alone. It's not always clear in the body of the draft whether the arsenic content in rice is determined before or after cooking or washing. The Consumer Reports studies are with dry rice, but the studies on p. 55 are with cooked rice. These data are not directly comparable. The data in Figure 5.1 (p. 69, Interrelationship of the Risk Assessment Model Components), has only rice and no water. Table 5.8 (p. 82) shows the effect of washing with deionized water on cancer risk but not the real-world situation, where there is a base-line of arsenic in all drinking water. The additive effect is addressed with pregnant women on p. 87, but on p. 81 a study from India is dismissed because the water had too much arsenic in it. Yet, most of the data on arsenic exposure are from populations such as the Taiwanese, where rice with relatively high arsenic content is a major

food source.

While most U.S. municipal water supplies are compliant with the 10-ppb MCL, according to the USGS Water-Resources Investigations Report 99-4279, four municipal water supplies for cities with populations of 100,000 to 1,000,00 and seven with populations between 50,000 and 100,000 have greater than 20 ppm arsenic. In addition, there are many people in the U.S. who depend on well water with high levels of arsenic. Even for populations exposed to the MCL, the effect of lifetime exposure to 10 ppb in drinking water (not only water used for cooking rice) should be added to the risk from rice. This is especially important when considering the linearity (or nonlinearity) of models at low exposure, where the actual exposure is undoubtedly larger when the contribution of food arsenic is added to the low dosage in drinking water. The fact that there might be an additive risk should be explicitly described.

7. Do you think the key findings and conclusions that we made are supported by the information provided in the risk assessment? If not, please explain what alternative findings and conclusions should be considered.

I agree that the key findings are supported by the information provided. The problem is that there is not enough information available on arsenic exposure in U.S. populations and on the quantitative effects of exposure on pregnant women, fetuses, infants and children. In the absence of these data, I agree with the Executive Summary (p. 2): "*We must substitute educated assumptions and professional judgment in these instances, based on the best available evidence*."

8. Do you have any other comments or suggestions that are not elicited by 1-7?

The market-share data (p. 46: Section 4.2.5 MARKET SHARE) on arsenic in rice is not broken down geographically. One suggestion is to limit where rice can be grown to low arsenic regions. Meharg has shown that rice grown in California has 41% less arsenic than rice grown in South Central states such as Texas and Louisiana (Williams PN, Raab A, Feldmann J, Meharg AA. 2007. Market basket survey shows elevated levels of As in South Central U.S. processed rice compared to California: consequences for human dietary exposure. *Environ. Sci. Technol.*, 41:2178-2183). In the southern states the fields were previously used for other crops such as cotton, which were sprayed with arsenic as a defoliant, greatly increasing the amount of arsenic for uptake into the rice grain.

Water management is a possible way to limit arsenic accumulation in rice (Hu P, Huang J, Ouyang Y, Wu L, Song J, Wang S, Li Z, Han C, Zhou L, Huang Y, Luo Y, Christie P. Water management affects arsenic and cadmium accumulation in different rice cultivars. *Environ. Geochem. Health*, 35:767-778 (2013). Flooded cultivation results in mobilization of arsenite, which is easily accumulated by the plant. With dry cultivation most of the arsenic is oxidized and immobilized by binding to iron minerals. However, rice takes up much more cadmium under dry cultivation, so there may be a trade-off between the two toxic metals.

There is also considerable research on selection of cultivars that accumulate less arsenic (Williams PN, Price AH, Raab A, Hossain SA, Feldmann J, Meharg AA. Variation in arsenic speciation and concentration in paddy rice related to dietary exposure. *Environ. Sci. Technol.*, 39:5531-5540 (2005) and Kuramata M, Abe T, Kawasaki A, Ebana K, Shibaya T, Yano M, Ishikawa S. Genetic diversity of arsenic accumulation in rice and QTL analysis of methylated

arsenic in rice grains. Rice (N Y) 6:3 (2013)).

III. SPECIFIC OBSERVATIONS ON DRAFT ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DOCUMENT

Page	Paragraph/Line	Comment
9	Paragraph 1	"*Once absorbed, inorganic arsenic is metabolized by reduction from AsV to AsIII in the blood and is taken up by cells in tissues, mainly the liver, followed by intracellular oxidative addition of methyl groups to form MMAV and DMAV*." This is inaccurate. Oxidation does take place in the reducing environment of the cytosol. If that were true, then methylated arsenicals would not be a health concern. In the cytosol, the methylated species are almost certainly the more carcinogenic and toxic trivalent species.
9	Paragraph 2	"*Two possible mechanisms have been proposed for the metabolic pathway of inorganic arsenic. . . ..*" A third mechanism was just reported that indicates that the products of AS3MT are toxic and carcinogenic. (Dheeman DS, Packianathan C, Pillai JK, Rosen BP. 2014. Pathway of human AS3MT arsenic methylation. *Chemical Research in Toxicology*, 27:1979-1989.)
9	Last paragraph	"*Ingested inorganic arsenic is excreted via the kidney within a few days as inorganic AsV and AsIII and as MMAV and DMAV, with lesser amounts of the trivalent methylated metabolites.*" Both X.C. Le and M. Styblo have shown that this is an artifact. In air urinary trivalent species are rapidly oxidized, but, with careful handling, they have been shown to be the more toxic and carcinogenic reduced species. (1. Del Razo LM, Garcia-Vargas GG, Valenzuela OL, Castellanos EH, Sanchez-Pena LC, Currier JM, Drobna Z, Loomis D, Styblo M. Exposure to arsenic in drinking water is associated with increased prevalence of diabetes: a cross-sectional study in the Zimapan and Lagunera regions in Mexico. *Environ. Health*, 10:73., 2. Gong Z, Lu X, Cullen WR, Chris Le X. 2001. Unstable trivalent arsenic metabolites, monomethylarsonous acid and dimethylarsinous acid. *Journal of Analytical Atomic Spectrometry*, 16:1409-1413.)
10	Paragraph 2	"*By measuring the relative amount of arsenic metabolites in urine, it has been shown that intracellular metabolism of inorganic arsenic involves extensive metabolism to DMAV and MMAV in most animal species, including humans*." Again, this is inaccurate. Measurement of urinary arsenic cannot show what the products of AS3MT are inside the cell. The products of arsenic methylation are almost certainly trivalent. (1. Dheeman DS, Packianathan C, Pillai JK, Rosen BP. 2014. Pathway of human AS3MT arsenic methylation. *Chemical Research in Toxicology*, 27:1979-1989., 2. Marapakala K, Packianathan C, Ajees AA, Dheeman DS, Sankaran B, Kandavelu P, Rosen BP. 2015. A disulfide-bond cascade mechanism for arsenic(III) S-adenosylmethionine methyltransferase. *Acta Crystallogr. D. Biol. Crystallogr.*, 71:505-515. 3) Marapakala K, Qin J, Rosen BP. 2012. Identification of catalytic residues in the As(III) S-adenosylmethionine methyltransferase. *Biochemistry*, 51:944-951
15	2.3.2	"*The arsenic-carbon bond is quite strong, and most mammalian species do not have the capacity to break it; thus, inorganic arsenic is not formed*

Page	Paragraph/Line	Comment
		during the metabolism of organic arsenicals." However, bacteria can break the C-As bond with the ArsI C-As lyase (Yoshinaga M, Rosen BP. 2014. A C-As lyase for degradation of environmental organoarsenical herbicides and animal husbandry growth promoters. *Proc. Natl. Acad. Sci., U.S.A*, 111:7701-7706.) It is possible that some microbiome bacteria can break down methylarsenicals. This has not been investigated.
22	Last paragraph	p. 42: *"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 at the individual level."* This is a serious concern since most studies on arsenic exposure are in populations where rice is a major food source.

IV. SPECIFIC OBSERVATIONS ON DRAFT ADDENDUM TO FDA'S ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DATED MAY 2014

Page	Paragraph/Line	Comment
-	-	The addendum is clear and comprehensive. I agree with the conclusion: "*none of this research is sufficiently developed to be useful in quantitative risk assessmen*t.

V. SPECIFIC OBSERVATIONS ON FDA ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT CANCER MODEL

Tab	Steps taken within the tab	Comment
Contamination	Types of rice	It would be helpful if the types of rice were further broken down into geographical regions. According to Meharg's market basket analysis, California rice has less than half the arsenic contamination of southern states rice.
Exposure	Ethnicity	I assume that the Asian population is lumped in with all other ethnicities. Considering that they consume the most rice of any ethnic group, they should have a separate tab.
Risk estimates	Survey year	It would be helpful to have predictions for future years. The U.S. Census Bureau estimates that the percentage of Hispanic and Asian populations will double by 2060, which suggests a large increase in future rice consumption and arsenic exposure through rice.

II. Reviewer #2

Peer Review Comments on Arsenic in Rice and Rice Products Risk Assessment:
Draft Report, Addendum, and Model

Reviewer #2

I. GENERAL IMPRESSIONS

The organization of the report is generally fine. I would like to see more details in the summary, particularly concerning the variation in exposure to inorganic arsenic through rice, the assumptions made for the cancer risk assessment, susceptibility factors, and non-cancer effects in pregnant women and children. The reading of the sections with summarized literature would be facilitated by structuring the text according to the outcomes.

The summary and the conclusions in the different sections give the immediate impression that FDA does not consider arsenic in rice an important problem, that there is no new literature suitable for risk assessment, and that there are few possibilities to lower the exposure. However, several of the conclusions are poorly supported by the text and the cited studies. At least it is not clear how. Considering the multitude of toxic effects of arsenic, including cancer and impaired child development (with considerable support in the document), and the many uncertainties in the risk assessments, I would recommend a first general conclusion that it is essential to limit the exposure to arsenic through all sources, including rice and rice products as much as possible. Then, the exposure information and data supporting the quantitative risk assessment(s) could be presented in quite some detail. Thereafter, can it be argued/concluded whether the exposure through rice is a problem, for the general American, as well as for high consumers and small children.

The document states that skin changes ARE the typical chronic effects of arsenic besides cancer. However, the prevalence is fairly low, even at high-level exposure through drinking water (Rahman *et al., EHP*, 2006). I think cardiovascular effects and diabetes are probably of more relevance for low-dose exposure from rice, especially during pregnancy. Also, available data on overall mortality, especially in the low-dose range, should be discussed. On the other hand, effects of short-term exposure are not really relevant for the present evaluation. I also miss a discussion of the potential impact of early-life arsenic exposure on health effects other than cancer later in life; see e.g., review by Farzan/Karagas *et al., TAAP*, 2013.

The thorough modeling of lung and bladder cancer risk based on the Chen *et al.*, 2010 studies is appreciated, but the limitations of those studies are not sufficiently considered. The estimates would be more reliable if they were: *i*) based on dose-response excluding the extremely high (and irrelevant) exposure levels; *ii*) supported by more data from previous cancer risk assessments (especially for drinking water); *iii*) supported by additional risk assessments based on other cancer studies (especially bladder cancer); and *iv*) given support from data on mechanisms of action in the low-dose range.

The presented estimations of the cancer risks from arsenic in rice are focused on mean concentrations and exposures. I would recommend them to be presented for different scenarios

of exposure to inorganic arsenic through rice, not only servings (especially if not defined), as well as the different risk factors.

The susceptibility factors would be easier to comprehend and to consider in the risk assessment if they were included in separate sections (age, gender, arsenic metabolism, genetic polymorphisms, immune suppression, smoking etc.). This will facilitate an estimation of the overall variation in health risks. Although the aim of this report is to evaluate the health risks of arsenic in rice, I miss a section on the presence of other commonly occurring pollutants in rice, e.g., cadmium, and the potential interactions with arsenic concerning the various adverse health effects.

The presentation of the low-dose effects of early-life exposure is essentially without specific information, and the firm conclusion (section 2.6.1, page 23.) that the uncertainties in the exposure of pregnant women make it impossible to arrive at a TDI is not motivated. Further, I cannot see that the statement is supported by the reviewed studies in Appendix 9.13. Also the similarly firm conclusion concerning limitations in the studies of exposed children (section 2.6.2, page 25) is not supported by the cited studies, and also not clearly motivated in the text. The sections should improve markedly by introducing summaries and critical evaluations of the Appendix data and then motivating the overall conclusions based on that.

II. RESPONSE TO CHARGE QUESTIONS

1. The risk assessment focuses on the risk associated with consumption of rice and rice products.

1.1. Have we adequately explained why FDA focused on these foods?

Appears ok.

1.2. If not, what additional information should we provide?

[The reviewer did not comment.]

2. Although we did not conduct a comprehensive literature search of all publications on all aspects of arsenic, we relied upon and cited other sources that have extensively reviewed the literature. Additionally, we included the newer research being published, especially on susceptible populations. With this in mind, did we include all pertinent recent literature?

It is certainly appreciated that these types of evaluations have to rely on other sources that have extensively reviewed the literature, mainly from ATSDR, EPA, etc., but also review articles in the scientific literature (although these must be critically evaluated). However, there are quite a few original articles cited and mostly it is not clear from the text whether the citation concerns an original study or data reviewed by someone else. It would facilitate the understanding if "as reviewed by" is added in the text whenever a review article is cited, unless it is obvious from the reference, e.g., EPA, FDA etc. Also, it is not always clear why a specific original study has been cited. Often, there are several other articles with more or less deviations in the provided information or conclusions. Because there are so many articles published on different aspects of

arsenic, the selection of only one may be misleading. Concerning details not essential for the present valuation, it may be better not to provide any statements.

As to additional comprehensive overview reports, I miss the following:
-EFSA 2014: Dietary exposure to inorganic arsenic in the European population (EFSA Journal 2014; 12(3):3597; www.efsa.europa.eu/en/efsajournal/doc/3597.pdf). In particular, this is a useful example of how to express not only the nation-wide mean exposure, but also a measure for high consumers (95th percentile).
-NRC 2001: Arsenic in drinking water, 2001 update. This is still the most comprehensive cancer risk assessment for arsenic; and it was the basis for the lowering of the U.S. drinking water standard to 10 µg/L. Therefore, it would be pertinent to include a comparison of the quantitative cancer risk with that provided by NRC 2001, e.g., on page 38.
-Yorifuji/Grandjean, *J. Natl. Cancer Inst.*, 2010 and *EHP*, 2011; Smith *et al.*, *EHP*, 2006 and 2012; Steinmaus *et al., Cancer Epidemiol. Biomarkers Prev.*, 2014.
- The important series of experimental studies by Michael Waalkes group, not the least Lung tumors in mice induced by "whole-life" inorganic arsenic exposure at human-relevant doses. *Arch. Toxicol.*, 2014; 88(8):1619-29.
-The review by Boekelheide *et al.*, *EHP*, 2012 may be useful. It provides support from studies on early-life arsenic exposure and epigenetic alterations (some of which are included in non-cancer section on page 6-10 in Addendum 2015).

I also miss a discussion of other chronic effects of arsenic than cancer, especially cardiovascular effects and diabetes, for which there may be data to support quantitative risk estimation; see e.g., studies and review articles by the research group of Dr. Navas Acien. Also there is a recent study from New Hampshire, indicating cardiovascular effects of low-dose arsenic exposure (Farzan *et al., TAAP*, 2015; *EHP*, 2015).

3. Do you agree with the dose-response modeling approach, data selected, and assumptions that we used for assessing the lung and bladder cancer risk estimates?

3.1. If not, what alternative modeling approaches should we consider? Specifically we are interested in comments on the model weighting used. For example, how much weight should be given to the different alternative models and what is your scientific rationale for the choices?
3.1.1. Additionally please comment on whether our use of the Morales model is consistent with the way it was used in developing the EPA 2001 Drinking Water Rule.

Without going into details concerning the different statistical models, I would like to express my concern about the chosen dose-response modeling, as well of the selection of only the Chen study (2010) on bladder cancer, in particular. The Chen studies have obviously certain strengths (e.g., prospective cohort and fairly large size), but also several limitations. Because of the short follow-up period (11 years), it includes only 45 incidences of urinary tract cancer; 8 of which had unknown water arsenic concentration. The 37 cases with exposure data are evaluated against 5 categories of arsenic exposure based on arsenic concentrations in the well water, which ranged from below 0.15 to more than 3,000 µg/L. Besides the mentioned assumed 2-4 liter of water consumed daily, it is not quite clear how the water concentrations (at baseline or whole period?) were transformed to the doses presented in table 3.3. The last paragraph page 30 and the first on page 31 needs to be expanded and the assumptions clarified. What is for example 76±2? Is the

precision in the estimates such that a decimal is suitable? How was the dietary intake of arsenic estimated, and what was it (per age and gender)?

Another important point is the use of the whole range of exposure (drinking water concentrations) in the Taiwanese study. Looking at the fit of the dose-response for both bladder and lung cancer, there appears to be a change in the slope somewhere between 10 and 30 µg/kg bw/day, indicating a steeper slope of the dose-response at the lower dose range (below 10 µg/kg bw/day), compared to higher dose levels. This is clearly shown in Figure 9.17, based on the Hill model, and in Figures 9.20 and 9.21, based on "Best dose-response model for bladder cancer." Such a non-linear dose-response would fit well with mechanistic data indicating increased cell proliferation at very low arsenic doses, but rather apoptosis and cell death at high doses (e.g., Schwerdtle *et al.,* 2003; Soucy *et al.,* 2003; Ferrario *et al.,* 2008, and others). This is, however, not clearly discussed in section 2.2.1.

Of major concern with the chosen modeling is that the highest data point, µg/kg bw/day, which is indeed influential in the dose-response, is way above the doses of relevance for the present evaluation of exposure through rice, i.e., about 0.1-0.2 µg/kg bw/day. The high-dose level represents Taiwanese individuals with drinking water concentration up to >3 mg As/L (defined as >300 µg/L in the original article by Chen *et al.*, 2010 and as average 836 µg/L in the current document). With drinking water concentrations of 0.5-3 mg/L or more, a water consumption of 2-4 L/day would result in an intake of *several mg of arsenic per day*; which is closer to the doses used in cancer treatment (3-10 mg As_2O_3/day for 1-2 months) than to the intake of a few µg of As/day via rice. Thus, considering the mechanistic data concerning dose-dependent cell proliferation and apoptosis, one would in fact expect an inverted U-shaped dose-response when modeling over such wide dose ranges. In this context, I would like to refer to the indicated reduction of the breast cancer risk in relation to very high concentrations of arsenic in drinking water, complemented with documented apoptosis in breast cancer cell culture studies *in vitro*, in the recent study by Smith, AH, *et al.*, 2014 (*EBioMedicine*). There is also support from experimental cancer studies in mice, e.g., by Michael Waalkes, *Arch. Toxicol*., 2014: "In male offspring mice, arsenic exposure increased ($p<0.05$) bronchiolo-alveolar tumor (adenoma or carcinoma) incidence at 50 ppb (51%) and 500 ppb (54%), but not at 5000 ppb (28%) compared to control (22%). These arsenic-induced bronchiolo-alveolar tumors included increased ($p<0.05$) carcinoma at 50 ppb (27%) compared to controls (8%). An increase ($p<0.05$) in lung adenoma (25%) in the 50-ppb group compared to control (11%) occurred in female offspring."

The uncertainty in the chosen dose-response for bladder cancer in the present report is further supported by the quite large differences compared to previous risk assessments (including NRC 2001). *I would suggest restricting the dose-response modeling to the 4 first points, which anyhow cover quite a range in exposure. Because of the limitations in the chosen study, it is also recommended to carefully compare the estimates with those based on the data from south-west of Taiwan, used in previous comprehensive risk assessments, and to adjust the uncertainties according to the results.* In particular, the estimates should also be compared (e.g., on page 38, Table 3.5) with the cancer risk estimates presented by NRC 2001 and EFSA 2009, as well as the present drinking water standard. Importantly, the differences in the risk estimate relative to the previous cancer risk assessments, including the previous from FDA on arsenic in apple juice (page 38) needs to be commented upon in more detail (page 34). Comparison should also be performed with the more recently published cancer studies on arsenic, most of which are cited in the Addendum 2015.

It is questionable to apply the same risk model for estimating the cancer risk of exposure during infancy and early childhood (page 93 and in summary pages 3-4), without considering the likely higher susceptibility. The presentation of the risk with one decimal (Table 7.1, page 93) gives the impression that the estimate is very accurate, when in fact it is highly uncertain.

3.2. Given the challenges of using epidemiology data for dose-response modeling and especially in this case, using data from non-U.S. population, please comment on whether FDA adequately justified the selected studies (Chen et al.). If not, what additional information should we provide in the report?

The weaknesses of the Chen 2010 studies, particularly the one on bladder cancer (see comments above), and the related uncertainties in the cancer risk assessment for arsenic exposure from rice, ask for a more thorough discussion and presentation in the overall summary. The main problem is not that it is a non-U.S. population (!), but rather that the follow-up time was short, providing few cases, and that the current dose-response modeling included extremely high exposure data. The provided summary on pages 2-3 does not reflect the inherent uncertainties and the required prudence in the formulation of the risks, the risk factors and population groups with increased susceptibility or risks (due to high exposure). See further my comments above under point 2.

4. For prenatal and early life exposure, are there enough data of sufficient quality to develop a dose-response model and quantify the risk estimate for these two exposure periods (life stages)? If not, do you have suggestions to strengthen the text and to assist in the estimation of risk for adverse pregnancy and developmental outcomes?

As the FDA report concludes (page 25) that "the limitations in the studies make them unsuitable for the development of a TDI", it would be pertinent that these "limitations" be described and clearly motivated. Either the limitations in each separate study could be commented on in the summary, or this could be done (in quite some detail) in the main text of the report.

I do think, however, that it would be possible to obtain some quantitative risk estimates concerning arsenic-exposure and impaired birth weight and neonatal/infant mortality, possibly also immune effects/infections and child development/neurotoxicity. Indeed, it would be important for the present risk assessment, considering the indicated frequent consumption of rice among pregnant women and young children. In contrast to what is stated in point 2, page 11 of the Addendum, I think there is evidence indicating adverse effects below 50 μg/L in urine (likely corresponding to less than 50 μg/L in drinking water, depending on the contribution from food).

Although my review of the FDA document does not allow for a comprehensive re-evaluation of the literature and quantitative risk assessment, I'll discuss birth weight as an example, mainly referring to the studies cited in the meta-analysis by Quansah (cited in the Addendum, page 4, last paragraph). For the largest prospective cohort study on arsenic exposure and birth weight (n=1578 women, urinary arsenic measured in early pregnancy), by Rahman *et al.* (2009), only the difference in birth weight between women with urinary arsenic > and <100 μg/L is reported by Quansah *et al.* However, in the original article it is stated that "… a significant dose effect was found with birth weight in the lower level of exposure. In this range (0–100 μg/L) of exposure, each 1-μg/L increase in urinary arsenic concentration was associated with a 1.68-g reduction in birth weight." (which is cited in Appendix 9.13). The effect was robust and didn't

change much by adjustment for multiple potential confounders and effect modifiers. Looking at the data in more detail, including the scatterplot of all data, the slope was indeed linear, and no threshold was indicated. To note, urinary arsenic reflects exposure from all sources, including rice. In fact, rice was likely the main source of arsenic exposure below about 50 μg/L in the urine. A strong support of a low-dose effect on birth weight can be obtained from the third study in the meta-analysis, in which 424 infants born to mother using water with on average 40 μg/L in Antofagasta, Chile, had a 57 g lower mean birth weight (95% CI -123 to 9), than 420 newborns in Valparaíso, with <1 μg/L in the water (Hopenhayn *et al.,* 2003). Further support can be found in the much smaller New Hampshire study (n=133 pregnant women; Fei *et al.,* 2013; mentioned only in the text page 416 in Quansah *et al.*), which indicated an inverse association between maternal urinary arsenic (median 4.4 μg/L; IQR 1.8-11.9 μg/L) and birth weight (-1.3 g per μg/L), although that not a primary aim of the study, which focused on placental expression of genes of importance for fetal size. However, that information does provide some mechanistic support. In a more recent study from New Hampshire (n=223 pregnant women with exposure data), Davis *et al.* (2002; not cited in the current FDA report) concluded that a 1 μg/L increase in maternal urinary arsenic concentration (ranging from 0.0 to 22.0 μg/L) was associated with a decrease of 0.047 (95% CI: -0.115, 0.021) in head circumference and 0.072 (95% CI: −0.151, 0.007) decrease in biparietal head diameter Z-score." I also miss the similar, but much larger (n=1929) cohort study on urinary arsenic concentrations and fetal growth (ultrasound) by Kippler *et al.* (*Repro. Toxicol.,* 2012), indicating arsenic-related impairment of fetal growth in the Bangladeshi cohort (same as the one studied by Rahman *et al.* (2009)) for birth outcomes. The impairment of fetal growth by arsenic was mainly seen in the higher SES families, supporting the effects observed in the U.S. study. Importantly, the study by Kippler *et al.* (2012) also provides strong indications of adverse effects of dietary cadmium on fetal development. The main source of cadmium, another toxic and carcinogenic metal, in the general population is rice, and the potential effects of the combined exposure should be considered. Obviously, this is particularly important concerning the early-life exposure. I may also mention that there is an additional study from Shanghai indicating an association of maternal blood arsenic and birth weight in Shanghai, China (Xu *et al.,* 2011). However, it is published in a Japanese journal that I cannot get (abstract in PubMed though). In addition, there is support for early-life effects from studies on kinetics and mechanisms.

Back to the meta-analysis by Quansah *et al.*: The second study included in the meta-analysis of arsenic and birth weight (Huyck *et al.,* including 49 women only) and the fourth study, by Yang *et al.* (2003), given the highest weight (57%) because of the size, cannot be used for the estimation of low-dose effects on birth weight. The Yang study is an ecological study with exposure contrast between 18 villages in northeastern Taiwan, with arsenic concentrations ranging from <0.15 to 3,590 μg/L in the well water (30% of the 3901 wells above 50 μg/L), and villages without history of arsenic exposure, including the Taipei metropolitan area (below 0.9 μg/L). The newborns in the villages in the northeast (n=3872) were on average 29 g lighter (based on register data) than those in the villages in other areas of Taiwan without known arsenic exposure through drinking water (n=14,387). However, due to the ecological design and the wide range of water arsenic concentrations in the exposed group, the study should not have been included in the meta-analysis with the cohort studies. Another study mentioned in the text only (page 416, right-hand column, top paragraph), the study by Guan *et al.* (2012), was cited as showing 0.22 kg(!) lighter newborns of mothers with U-As >5.3 μg/L, compared to those with U-As <5.3. However, that study did not include measurements of urinary arsenic; instead the exposure was based on concentrations in maternal blood (> vs. <5.3 μg/L). This makes the

results somewhat more reasonable (the linear regression analysis indicate -0.02 kg/µg/L in maternal blood), although the very large effect is difficult to evaluate as only 125 mother-infant pairs were included. Also, the potential presence in blood of much less toxic organic arsenic compounds from food, might have overestimated the exposure to inorganic arsenic (thus, underestimating the effect of inorganic arsenic). *Together these shortcomings emphasize the need for careful evaluation of the original articles for evaluation of suitability in the health risk assessment, just as was done in the report for the cancer risk assessment. In particular, I would recommend a re-evaluation of potential low-dose effects for size at birth, stillbirth and neonatal/infant mortality.*

Also immune effects of arsenic, especially developmental immunotoxicity, have been reported from several countries, including U.S.A., with good exposure data in the low dose range. There are indeed different outcomes, including morbidity in infectious diseases, immunosuppression and markers of inflammation, supporting causality. Although the data may not be suitable for straight-forward dose-response calculations (as was done for cancer), it would most likely be possible to conclude that the effects occur at fairly low exposure levels, and to try to specify that.

5. Do you agree with our approach to exposure assessment, including the data and assumptions used. If not, what alternative approaches, data or assumptions should we consider?

The document presents quite a lot of useful information on arsenic exposure from rice and rice products (Pages 41-67, + several appendices). Still, very little is presented in the summary on page 2; in fact only the mean concentrations in four types of rice are reported. Even the section 4.4 presents mainly the mean values of the concentrations of arsenic in rice, the mean consumption of rice (per capita and per serving), and thus, the average risk.

In particular, the exposure and associated health risk for different segments of the population is not adequately considered. Instead of only reporting the average concentrations for white and brown rice, *I would suggest including a summary table(s) with both mean/median values and ranges (or 95th percentiles; as done by EFSA 2014) of: i) concentrations in rice and rice products; ii) rice consumption (per serving and per day; for all people and for infants); and iii) the resulting variation in the exposure to inorganic arsenic as µg/kg bw/day or serving. For infants, it is recommended to present rice milk/beverages separately, as the consumption may be quite high.* As an example, I find very informative presentations in the recent publication by Signes-Pastor *et al.* (Table 4 Figure 2 in Inorganic arsenic in rice-based products for infants and young children, Food Chemistry, in press http://dx.doi.org/10.1016/j.foodchem.2014.11.078). Such a detailed summary of the exposure certainly facilitates the understanding of the health risks for different segments of the population.

6. Do you agree with the assumptions and scenarios we presented in the "What if?" section of the risk characterization?

6.1. Are there other scenarios that should be included? If so, please explain why and provide details about the additional scenarios for FDA to consider.

In the following I mainly comment on the conclusions as they are presented in the initial summary section, but the same arguments are of course valid for the corresponding main

sections in the report.

Summary, page 3, third bullet: Specific information on how cooking practices may decrease the exposure to arsenic should be mentioned. The comment that "these practices" (whatever is meant by that) may reduce the intake of certain nutrients (the intake of which from rice is usually not very important) is quite out of place. If mentioned, it should be quantified. Nevertheless, what is most important: to decrease the cancer risk or to get a slightly lower intake of some nutrients? In any case, the fraction of this loss relative to the RDA should be provided. I think it is a very important task of this document to provide information on how the consumers can decrease their intake of arsenic from rice. I would like to refer to the very recent discussion (with further citations) in Nature July 22, 2015 (Emily Sohn: Simple cooking methods flush arsenic out of rice. Preparing rice in a coffee machine can halve levels of the naturally occurring substance. http://www.nature.com/news/simple-cooking-methods-flush-arsenic-out-of-rice-1.18034)

Summary pages 3-5, the third bullet on page 3, the two last bullets on page 4 and the two on top page 5 all concern potential means and methods of reducing exposure to inorganic arsenic from rice and related cancer risks. It would facilitate to have these bullets together with an appropriate sub-heading. I would suggest *an initial statement about the need to minimize as much as possible the arsenic content in all foods, including rice and rice products, considering the multitude of health effects of arsenic, including cancer and probably impaired child development, even at low exposure levels. This is particularly important for rice and rice products intended for young children, who seem to be particularly at risk.*

Concerning Table 1; it is not clear if the risk reduction relates to the nation average exposure or a specific intake of rice (the latter would be most suitable). Please, clarify.

The last bullet on page 4 is a strange one to include in a health risk assessment. It may as well be argued that recommendation or standards concerning are likely to decrease the arsenic concentrations in the products on the market.

The first bullet on page 5 (second paragraph) is redundant; repetition from second bullet page 3.

Second bullet, page 5 (summary): Dietary guidance is often difficult to follow, especially for people who frequently eat rice. It is probably even more difficult for infants and children who tend to have a less varied diet than adults (Page 19, third paragraph). Does the estimated reduction of the life-time cancer risk (6-23%) include this and the likely increased cancer risk for early-life exposure? If not, the uncertainty must be pointed out. Also, if people are recommended to decrease the intake of rice, they need recommendations about what else is appropriate eat; see further my comment iv below. In this context, it is essential to discuss alternatives to rice for infants and children who require a milk- and/or gluten-free diet, who potentially are more susceptible to both arsenic and other frequently occurring pollutants.

Obviously, limiting people's exposure to dietary arsenic requires many coordinated measures. The food producers at different levels should, by different means possible, minimize the presence of inorganic arsenic in food, particularly infant and child foods. It's also important to raise public awareness to facilitate an informed choice of food, which will further encourage low-arsenic products on the marked. In this context, I certainly miss formulation of measures like:

i) Consumer information through labelling the various rice and rice products with the arsenic content (concentrations) and through general information on FDA web site etc.;
ii) Information about methods for lowering the arsenic content through cooking methods (mainly cooking in plenty of water); this could also be recommended to the producers of various rice products.
iii) To request/recommend producers to use consistently low-As rice for infant and child foods.

To inform both consumers and producers about alternative cereals for infant and child food, e.g., maize, wheat, oat, sorghum, millet etc. I would recommend an additional table in Appendix 9.1 concerning total and inorganic arsenic in different types of grains, probably available in the FDA database; information could probably also be provided by Professor Meharg, Institute for Global Food Security, Queen's University Belfast, Belfast, Northern Ireland.

7. Do you think the key findings and conclusions that we made are supported by the information provided in the risk assessment? If not, please explain what alternative findings and conclusions should be considered.

Several issues concerning poorly motivated statements and conclusions have been raised in the comments above. Here I provide comments specifically on the statements on pages 97-98:

Point 2: As mentioned above, the ranges of concentrations are as important as the mean values. Also, the ranges in the intake of arsenic per serving (average size) and per day should be given, by different types of rice consumed, and for infants and all consumers. The last sentence is ok.

Point 3: Preferably, something about the related health risks could be provided.

Point 4: First, as mentioned above, I fear that the cancer risk is underestimated, particularly for susceptible population groups (which should be specified in the key findings). Second, the indicated risk (at present 39/1,000,000) should be related to a specific intake of inorganic arsenic, e.g., one serving a day (with corresponding assumed intake of arsenic specified). Third, a comparison with all cancer cases, mainly caused by smoking (as mentioned bottom page 17), is not appropriate. Comparison, if any, should be with diet-related cancer risks. Also, the main risk and uncertainty factors should be mentioned (separate point). To note, even the estimated cancer risk per capita is higher than what is usually considered acceptable for a single chemical (1/100,000).

Before the report goes into the details of cancer risk in the risk assessment report, I think an important more general key point would be to mention that chronic exposure to inorganic arsenic may cause a multitude of adverse health effects, including cancer and impaired child development, and this is why the exposure through drinking and food should be minimized as far as possible.

Point 5: I suggest deleting the strange proposal/scenario to eliminate totally rice grain and rice products for infants and children. How would that be possible? What should they eat? Instead, it is recommended to present the potential risk reduction for limiting the intake to e.g., one serving a day. Even when recommending a decrease in the rice consumption, some information about

suitable alternative food must be provided, including the amount of arsenic that would cause. How about infants and children requiring a milk- and/or gluten-free diet?

Point 6: I have the same comments as above; it should be clear for whom these risk reductions apply. Obviously the risk reduction would differ depending on the amount and frequency of rice consumption; and what other food is consumed instead of rice. Relating it to the average American is of little help for the actual rice consumers. The highly uncertain assumption that a certain standard would remove a specific fraction of the products from the market does not belong in a risk assessment.

Point 7: Good point, especially the first part (lowering the concentrations), although this should be separated in terms of risk reduction (mentioning also other adverse effects of early life exposure). I would suggest presenting the risk reduction of lowering also to 50 µg/kg (or µg/L for beverages, which can be consumed in large amounts). It is obvious from table 9.13 that it is possible to obtain low-arsenic rice. Also the estimated risk reduction of lower consumption frequency, which I think is much more difficult, should provide more examples. For children eating rice cereals 3 times daily, it would be very hard, if not impossible, to reduce it to twice a week! Again, what is the most suitable alternative food?

Point 8: Cooking practices that are shown to decrease arsenic exposure should be mentioned. The cancer risk is obvious (or should be) from the previous statements. Note that there are recent studies on this issue.

Point 9: Why give an example of increasing risk at increasing consumption when the point is decreasing the amount of rice consumed. In this context, the commonly low compliance to food recommendations should be mentioned.

8. Do you have any other comments or suggestions that are not elicited by 1-7?

I would suggest changing from ppb/ppm to µg/mg per kg or liter. The ppb system is really out of date. A main disadvantage is that it doesn't explain if the unit is per kg or liter of the samples measured.

III. SPECIFIC OBSERVATIONS ON DRAFT ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DOCUMENT

Due to the size of the document and its scope, and the many general comments, the short review time has not allowed for line-by-line comments. In the following I provide my most important specific observations.

Page	Paragraph/Line	Comment
2-5	Summary	The main assumptions and uncertainties in the cancer risk assessment should be mentioned also in the Summary pages 2-5. In addition, as mentioned below, the results of several exposure scenarios should be presented, not only mean values.
2-5	Summary	Additional information in the summary should include the various risk factors such as certain genotypes, poor nutrition, synergy with other exposures, and exposure in early life. Even though the exact modeling of these factors has not been resolved (addendum July 2015, page 17), some

Page	Paragraph/Line	Comment
		estimates concerning how these factors could affect the risk estimates, based on certain assumptions, could be given. It would be of interest for the reader to know if it is a factor 2 or 10 or 100. Most importantly, they should be mentioned in the summary.
2	Summary, 5th line	The statement that "current research suggest that MMA and DMA, when present in food, are not readily absorbed" must be a mistake. See the correct evaluation on page 10, 3rd paragraph.
3	Summary	The cancer risk shouldn't only be presented per serving of rice, but also in relation to the estimated intake of inorganic arsenic. As for the risk per serving, the underlying assumptions should be mentioned. The reader should be able to relate specific rice consumption and a specific arsenic exposure to an estimated cancer risk. See further comments below on the exposure assessment and presentation
3	Summary, first paragraph	The comparison of the estimated cancer risk "attributable to lifetime exposure to all rice and rice products" (should be inorganic arsenic in rice and rice products!) with the total prevalence of lung and bladder cancer in the nation is not appropriate. First, it should be clarified if this is based on average exposure per capita or in rice consumers. Secondly, a major risk factor for these cancer forms is smoking (indeed mentioned on pages 17-18). Thus, the estimated risk should be compared with the cancer risks attributable to the diet and to the paradigm that an "acceptable" cancer risk from each single chemical/pollutant is 1/100,000, or 1/1,000,000; considering the large number of environmental carcinogens. The same comment goes for the similar statements in the main chapter. As an example of additional comparison, the estimated mean iAs exposure per serving of 0.1-0.2 μg/kg bw (page 61) would correspond to an intake of 7-15 μg iAs for a 70-kg person consuming one serving a day; which is similar to the intake through one liter of drinking water at the current drinking water standard of 10 μg/L, also based on the estimated risks for bladder and lung cancer (NRC 2001). Importantly, a high prevalence of a certain disease is no reason to accept specific risk factors.
3	Summary, second paragraph	Rather than saying that "If the amount was increased to an average of one serving a day," I would suggest presenting the risk for those who do eat more rice more often, e.g., 1 and 2 servings a day; and, preferably, the 95th percentile of the intake of inorganic arsenic from rice. Alternatively, something like "According to the current risk estimation, the consumption of one serving of XX g rice/kg bw per day would correspond to a lifetime risk of 74-165 cancer cases per million people, depending on the type of rice consumed. See for example Oberoi S *et al.* The global burden of disease for skin, lung, and bladder cancer caused by arsenic in food. *Cancer Epidemiol. Biomarkers Prev.*, 2014. Obviously, a clear presentation of the cancer risk in relation to specific arsenic intake(s) from rice (and the uncertainties) facilitates the understanding of the subsequent statements concerning exposure and risk reductions.
3	Summary, fourth bullet	Concerning the estimated cancer risk from exposure during infancy, the assumptions made should be provided in the summary. The modeling for Figure 1 should not only consider the limited time of exposure (which I think was the answer at the web conference), but also that young children have a much higher intake per kg body weight (3 times mentioned on page 19, third paragraph), and that early-life exposure likely increase the

Page	Paragraph/Line	Comment
		cancer risk later in life (section 2.4, pages 16-17). Given that rice is very common food in early childhood, and the potential importance of these risk factors for the overall risk estimation, section 2.4 should be expanded concerning the details of the "several studies" with references. To facilitate the reading, this section could come after the main cancer section (2.5). This issue appears not to be included in the Addendum 2015.
13	Section 2.2.3	I would recommend a more comprehensive discussion of other chronic effects of arsenic than cancer, e.g., cardiovascular effects and diabetes, for which there may be data to support quantitative risk estimation; see e.g., studies and review articles by the research group of Dr. Navas Acien. Also there is a recent study from New Hampshire, indicating cardiovascular effects of low-dose arsenic exposure (Farzan *et al., TAAP,* 2015; *EHP,* 2015). Thus, section 2.2.3 could be extended. Also, the potential indicated risk of health effects later in life due to early-life exposure should be mentioned as susceptibility factors (see review by Farzan *et al.,* 2013).
13	Section 2.2.3	I sincerely doubt the statement/conclusion in last sentence of 2.2.3. Indeed, 20 μg/kg bw/day (1.4 mg As/day for a 70-kg person!) is a very high dose. I would be very surprised if the cited IARC 2012 and EFSA 2009 have made such statements. As I read EFSA 2009: "A range of benchmark dose lower confidence limit (BMDL01) values between 0.3 and 8 μg/kg bw per day was identified for cancers of the lung, skin and bladder. . . ."
13	Section 2.2.3	The recently observed arsenic-related immune suppression in infants and children could be discussed in relation to risk factor for later cancer development. See further comment on this section in Addendum below.
4	Summary, first bullet	I recommend a similar diagram as Figure 2 for all life exposure (in the summary). See my comment above about recommended additional data on cancer risk at higher exposure levels (although the figures don't include anything else than mean arsenic concentration in rice and the mean serving size; which should be mentioned and discussed).
5	Overall summary	In the overall summary (page 5) referring only to the Japanese infant food poisoning incident as evidence of arsenic-related developmental neurotoxicity is not appropriate. Instead, the many studies pointing in the same direction of much lower exposures should be presented. I would suggest that reported dose-effect and dose-response estimations from the best studies are described and that an attempt is made to somehow arrive at a rough estimate.
10	Second paragraph	The first sentence needs a reference; I would suggest Vahter, *Toxicology*, 2002. This review article also concluded, based on multiple studies, that "the average relative distribution of arsenic metabolites in the urine of various population groups seems to be fairly constant, i.e., 10–30% inorganic arsenic, 10–20% MMA, and 60–70% DMA." The Caldwell study (2009) concerns the early NHANES arsenic speciation, which used a method that was not sensitive enough for samples of the general population. Also, comparing with the total arsenic in urine is not meaningful, as the fraction then is highly dependent on the presence of arsenobetaine and other organic arsenic compounds from seafood, in particular.
11-12	Section 2.2.1	Section 2.2.1 concerning mechanisms of action of arsenic, could be

Page	Paragraph/Line	Comment
		organized in a better way. The first and last paragraphs, as well as the second part of the next last paragraph (citing Kitchin and Conolly, 2010) deal with similar things and can be combined and, preferably, supported with some specific information. In particular, it is necessary to discuss the importance of the dose in relation to the mechanisms. It is well documented that very low doses induce cell proliferation, while high doses are more likely to induce apoptosis and even necrosis (see my comments on the cancer risk modeling above), but there is nothing mentioned about doses in section 2.2.1. Also, the lengthy discussion about DMA carcinogenesis should consider the doses used in the studies (especially for DMA and bladder cancer), the fact that DMA is a strong buffer, and that rats differ from all other species studied, concerning the kinetics of arsenic. I would recommend a summary at the end of this section concluding how the low-dose risk assessment can be supported by the mechanisms of action.
11-12	Section 2.2.1	As mentioned elsewhere, I don't think the study by Argos *et al.,* 2010, concerning arsenic-related mortality in an area of Bangladesh has anything to do with mechanisms of action.
12	Section 2.2.2	Section 2.2.2, page 12, can be omitted as short-term exposure is not relevant for the present evaluation.
12	Second paragraph	One study is (by mistake?) reported on page 12, second paragraph, although that section concerns mechanisms of toxicity. The statement that no effect on mortality was observed below 150 µg/L in drinking water needs to be supplemented by other studies finding increased mortality at even lower exposure levels in a previous, much larger study from Bangladesh (Sohel *et al., Epidemiology*, 2009).
13	Section 2.2.3	The section on effects of chronic exposure, section 2.2.3 needs to be extended; especially concerning cardiovascular effects and diabetes, for which there are data in the low-dose range (see more details above, page 2). Such effects might be particularly serious during pregnancy, and arsenic-related increase in blood pressure during pregnancy has been reported (see e.g., Farzan *et al., EHP,* 2015). Also, arsenic-related mortality should be discussed.
14	First two lines	The statements that the major source of evidence for human carcinogenicity comes from studies in areas where "exposure from drinking-water greatly exceeds exposure from dietary sources" and "where the range of drinking-water concentrations exceed 100 ppb" are not clear. Obviously, *the upper range* of arsenic concentrations in drinking water was often much higher than 100 µg/L, however, the total range usually started at much lower concentrations.
14	Second paragraph	In order to evaluate the non-significant OR at 90-335 µg/L as no increased risk of bladder or lung cancer, more details would be needed and, in particular, the sample size. The study (Steinmaus *et al.,* 2013) included 232 bladder cancer cases and 306 lung cancer cases and 640 age- and gender-matched controls. The adjusted bladder cancer ORs from the lowest to highest quartile of exposure were 1.00, 1.36 (CI: 0.78–2.37), 3.87 (2.25–6.64), and 6.50 (3.69–11.43), respectively; and the second represented lifetime average water concentration (before 1971) of 11-90 µg/L. It appears to be a highly significant trend. Obviously, Prof. Steinmaus may provide more information; also whether this study would

Page	Paragraph/Line	Comment
		provide a complement to the Chen 2010 study for dose-response estimation.
14	Third paragraph	The first two lines in this paragraph refer to two detailed reviews; what were their conclusions?
14	Third paragraph	In relation to the referred study of increased risk due to polymorphisms, I would recommend adding data on the risk increase due to genetic variants of the even more influential AS3MT gene. See e.g., Beebe-Dimmer *et al.*, 2012, Chiang *et al.*, 2014, Engström *et al.*, 2015
16-17	Section 2.4	*Concerning early life exposure and health risks*, I'm concerned about the many statements and conclusions without specific motivations or references. I'm not clear about the aim of section 2.4; I think it should either be deleted or expanded and moved to the cancer section.
16-17	Section 2.4, last two lines	The last two lines on page 16 and the two first on page 17 appears to concern latency time rather than susceptibility and would fit better in section 2.5. Also other sentences in 2.4 would fit better in 2.5, preferably forming a part on susceptibility factors.
17	Section 2.4, second half of second paragraph	The second half of the second paragraph page 17 is indeed questionable. A statement that children are not particularly susceptible would require a more thorough discussion with proper references. It is also in contrast to the writing on page 19. Concerning the increased cancer risk due to early-life exposure, please see further my comments and recommended additional literature under point 3.
19	Section 2.6, second paragraph	The reference to Myers *et al.*, 2010 is probably wrong. A reference to placental transfer could be the review by Vahter in *Annu. Rev. Nutr.*, 2009 (Effects of arsenic on maternal and fetal health). This could also be mentioned in the fourth paragraph this page, where it is stated that there are no reviews regarding health effects during pregnancy. Farzan *et al.* (*TAAP*, 2013) is another more recent review article.
21-23	Section 2.6.1	Section 2.6.1 is confusing. I would recommend moving the text from Appendix 9.13 to here and to make a more comprehensive conclusion based on the summaries. The very first paragraph in 2.6.1 provides a short description of the type of studies performed, not anything about the findings. The following sections concern the selection of the literature, which would fit better in a separate chapter.
23	Section 2.6.1, last paragraph	The last paragraph (page 23), which appears to be a conclusion, is not correct. Although the statement may apply to a few of all the reported studies, it is certainly not true for all, especially not when including the new information in the Addendum 2015.
24-25	Section 2.6.2, last paragraph	Also section 2.6.2 needs major revision. The last paragraph on page 24 and the first on page 25 are confusing. Which studies are discussed? Which are the studies using ecological design? Why is the exposure to arsenic in drinking water a problem here when most of the risk assessment is based on that? Similarly, why should studies using "total arsenic in the urine" (likely very few!) be criticized for not considering fluctuations in exposure? Which other exposure markers do consider that? Indeed, few studies have repeated exposure measurements, whether based on concentrations in water, urine or other media, but it would be a good idea to review those, in order to document an assumed variation in exposure. On the contrary, I think it is likely that the exposure through

Page	Paragraph/Line	Comment
		drinking water and frequently consumed food items is rather constant over time. Thus, on a group basis, urinary arsenic concentrations (preferably arsenic metabolites) usually reflect the ongoing exposure quite well.
25	Section 2.6.2, first paragraph	Also section 2.6.2 needs major revision. The last paragraph on page 24 and the first on page 25 are confusing. Which studies are discussed? Which are the studies using ecological design? Why is the exposure to arsenic in drinking water a problem here when most of the risk assessment is based on that? Similarly, why should studies using "total arsenic in the urine" (likely very few!) be criticized for not considering fluctuations in exposure? Which other exposure markers do consider that? Indeed, few studies have repeated exposure measurements, whether based on concentrations in water, urine or other media, but it would be a good idea to review those, in order to document an assumed variation in exposure. On the contrary, I think it is likely that the exposure through drinking water and frequently consumed food items is rather constant over time. Thus, on a group basis, urinary arsenic concentrations (preferably arsenic metabolites) usually reflect the ongoing exposure quite well.
25	Section 2.6.2, second paragraph	In the second paragraph page 25 "these studies" must be given references. Certainly, there are studies providing repeated measurements of both arsenic exposure and developmental measurements in the same study area and even in the same child cohort (see e.g., longitudinal analyses by Hamadani *et al.*, 2011). Also, the expressed concern about reversibility of neurotoxic effects should be expanded on with proper references, e.g., the Lancet series by Grandjean/Landrigan and Grantham-McGregor and others. In any case, the exposure through drinking water and food is certainly chronic.
25	Section 2.6.2, last paragraph	Concerning the statement in the last paragraph page 25, see my comments under point 4.
25	Section 2.6.2, last paragraph	I do miss a section on rice being an important component of infants and children who require a milk- and/or gluten-free diet. Are they at particular risk?
26-98	Sections 3-7	My specific comments on the cancer risk modeling are provided above.
-	Appendix I	Concerning the Appendix, I think 9.1 and 9.5 could be combined with 9.7-9.12, all with quite useful information.
-	Appendix I	Concerning 9.13, it would facilitate the reading to have a structure of all the summaries, e.g., according to outcomes. It is not always clear if the stated results, especially the dose-effect and dose-response relationships, are solely those of the original authors, or if they are also accepted by the FDA. There are quite a few dose-dependent effects reported, also in the low dose range (and even more in the original articles) without any additional comment or criticism. This makes it difficult to understand the FDA conclusions that the information is not enough for any quantitative estimates of the risks.

IV. SPECIFIC OBSERVATIONS ON DRAFT ADDENDUM TO FDA'S ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DATED MAY 2014

Page	Paragraph/Line	Comment
-	General Comments	Due to the size of the document and its scope, and the many general comments, the short review time has not allowed for line-by-line comments. In the following I provide my most important specific observations.
-	General Comments	The addendum on the more recent information is highly appreciated. Concerning the section on adverse pregnancy outcomes, it would facilitate the reading to include subheadings, or at least to organize the short summaries according to the type of publication and the effects concerned; e.g., for pregnancy outcomes, starting with review articles (Qansah *et al.*, 2015, + Bloom MS *et al., Int. J. Hyg. Environ. Health*, 2014), then fetal loss (Bloom *et al.*, 2014; although likely severely underpowered), birth size (Davis, MA, *et al., Environ. Health*, 2015; could be added; similar to that by Kippler *et al.*, mentioned above), potential mechanisms (Fei *et al.*, 2013), and biomarkers of exposure/susceptibility (Laine *et al.*, 2015, + Gardner RM *et al., Pharmacogenet. Genomics*, 2012).
4	Second paragraph	In relation to the described results of the Laine study, the marked change in arsenic metabolism (based on urinary metabolites) in early pregnancy should be mentioned (see e.g., Gardner RM *et al., Pharmacogenet. Genomics*, 2012). This is important information as it may lead to some protection of the fetus in late pregnancy.
4-5	Last/first paragraph	The summary of the systematic review and meta-analysis on arsenic and pregnancy outcomes by Quansah *et al.*, 2015is very short, mainly concluding that "arsenic in groundwater ≥50 μg/L was associated with increased spontaneous abortions, stillbirths, moderate risk of neonatal mortality and a significant reduction in birth weights." In the two last sentences on the short paragraph, it may not be clear to the reader what RA is, and which RA. Also, the statement "… agreed with the finding of no apparent adverse health effects from iAs in water at concentrations below 50 μg/L" is questionable. I don't think this meta-analysis and review really evaluated potential effects below 50 μg/L. Instead, they aimed for a cut-off for contrasting exposure at 50 μg/L (although in reality it differs markedly between studies). Also, there are several major problems and mistakes in this meta-analysis (see also my comments under point 4). The main shortcomings are the inclusion of studies of enormous variation in quality, inappropriate study design, and the wide range of cut-offs for the contrasting exposure in the meta-analyses. For further comments on this review, see my discussion under point 4 above.
6-9	-	The same comment concerning organization of the cited studies, as mentioned above, goes for the following section concerning new non-cancer endpoints. In particular, studies on immune effects need to be grouped, preferably directly after the first paragraph with relevant background information. Sorting from epidemiology to mechanisms would be useful. This would facilitate a discussion in the following section (Discussion, page 10). Similarly, studies concerning DNA methylation could be grouped. I miss studies on arsenic-related impaired growth (e.g., Saha *et al., EHP*, 2012; Gardner *et al., Am. J. Epidemiol*., 2013).

Page	Paragraph/Line	Comment
9	Next last paragraph	Concerning the summary of Rahman *et al.*, 2011, the statement that "the incidence of LRTI and severe LRTI was significantly higher in the highest quartile of exposure." is not correct. First, Rahman *et al.* used quintiles, not quartiles, of exposure (maternal urinary arsenic metabolites in pregnancy). Also, both LRTI and severe LRTI were significantly increased already in the second quintile, i.e., 36-61 μg/L in the urine, compared to those in the first (<36 μg/L). Importantly, the exposure was largely from rice in this exposure range. The summary should to be corrected and complemented with more details. The link between these effects on the risk of infectious diseases and infant mortality, as reported by Rahman *et al.*, 2007 (*Am. J. Epidemiol*., 165) and Rahman *et al.*, 2010 (*Epidemiology*, 21) would indeed be of interest. Furthermore, the findings have important support in the many studies on immune suppression, in the same cohort of children (Ahmed *et al.*, 2012, 2013, and 2014) and others. The studies by Ahmed are summarized on pages 6-7; however, the reported dose-effect data are poorly described, and needs revision. For example, the effects on infant thymus function apparently occurred at very low maternal exposure levels (Ahmed *et al.*, 2012:.". ln U-As (GW30) and ln B-As (GW14) were inversely associated with ln sjTRECs in CBMC (B = −0.53; 95% CI −0.93 to −0.13 and B = −1.27; 95% CI −1.89 to −0.66, respectively) below spline knots at U-As 150 μg/l and B-As 6 μg/kg.").
10	Top paragraph	I'm confused about the summary of Farzan *et al*. The maternal total urinary arsenic (should be arsenic metabolites, not total arsenic!) is stated to range 0.45-58.3 μg/L. Obviously the highest quintile could not be 262-977 μg/L, as stated on line 9. Apparently, this is taken from the discussion section in Farzan *et al.*, 2013, where the authors cite a similar, but much bigger study in Bangladesh (Rahman *et al.*, 2011; summarized just before Farzan *et al.*, 2013). Thus, the summary must be corrected.
11	Conclusion Nos. 2 and 5	Taken together the above studies could be considered for quantitative risk assessment, as I indicated in my comments under heading 4 above. Thus, I doubt the conclusion like No 2. Similarly, the sentence inserted as a separate paragraph after conclusion No 5, must be clearly motivated.
11	Addendum, conclusion No. 4	Concerning the conclusion No 4, concerning new data on neurodevelopmental effects, I think the "No" must be clearly motivated. It is not in line with the text on page 5. For example, in the summary of the study by Wassermann *et al.*, 2014, it is referred to the authors' suggestion that 5 μg/L might be an important threshold. However, there might be a power issue.
10-11	Conclusions	With these identified weaknesses in the summaries and the conclusions, I would recommend that all summaries include more data on the exposures/doses and the dose-effect relationships observed in the different studies cited, as well as an evaluation of the studies and the findings. Alternatively, the conclusions have to be more specific concerning the strengths and limitations of the available data.
17	Conclusions	Similar criticism can be applied to the conclusions presented on page 17. The fact that there is additional support for early-life exposure as an important susceptibility factor, and the new data indicating associations between arsenic exposure and other forms of cancer, should somehow be considered in the risk assessment (uncertainty factors; precaution, etc.). Indeed, it is essential, with a first overall conclusion in the overall

Page	Paragraph/Line	Comment
		summary concerning the increasing evidence for a multitude of adverse health effects of arsenic, even at fairly low exposure levels, which warrants decreasing arsenic exposure through rice as far as possible.

V. SPECIFIC OBSERVATIONS ON FDA ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT CANCER MODEL

[This reviewer did not provide any specific comments on the FDA Arsenic in Rice and Rice Products Risk Assessment Cancer Model.]

III. Reviewer #3

Peer Review Comments on Arsenic in Rice and Rice Products Risk Assessment: Draft Report, Addendum, and Model

Reviewer #3

I. GENERAL IMPRESSIONS

Overall, the FDA assessment of the risk of cancers from arsenic in rice is well constructed, and based on a fair and transparent evaluation of current literature. A strength of the assessment comes from adequate treatment of the models generated by Morales *et al.* and close agreement with the current EPA risk assessment. However, as discussed in the draft report, a weakness of the conclusions and the computer modeling is that neither the FDA model nor the Morales model are able to assess the true risk of low-dose exposure to arsenic from rice without a great amount of uncertainty. The extrapolation from the published dose-response relationships to the low dose range that causes the expansion of the confidence limit is a major limitation in providing an accurate assessment of the risk posed by arsenic intake from rice and rice products. The limitation is observed in the risk assessment cancer model, where the dose-response model does not go down to the expected range of exposures from rice that are predicted by the FDA exposure assessment. These limitations are only partially carried into the risk communication and conclusions regarding "what if" interventions. While factual in the percentages of risk reduction garnered by various reductions of arsenic in rice or the complete elimination of rice and rice products from the diet, the actual number of cancers or reduction of cancer risk is negligible given the low rate of cancers attributed to the arsenic in rice. The inference is that eliminating rice and rice products from the diet would reduce cancer risk, however, little or no consideration is given to the health benefits of rice that may even mitigate arsenic risk. The risk assessment is not based on arsenic in food containing a number of mitigating constituents and is rather based on a possible flawed assumption that exposure to arsenic in food is equivalent to arsenic in water that does not contain mitigating constituents.

The overall value of the assessment of non-cancer disease risk is minimal given the limitations of not providing a fully rigorous dose-response analysis for either the birth outcomes or cognition. It is not evident that the FDA used all of the possible current literature that may have supported the needed dose-response analysis, and both the addendum and text of section 6 suggest that new data sets are or may soon be available to produce a rigorous assessment. It is not evident why the FDA went to the tier 3 endpoints that were suggested by the NRC report as this tier was characterized as being poorly supported by adequate low-dose-response studies. Tier 1 included cardiovascular disease where there are adequately powered prospective epidemiological studies that define the low end of the dose-response curves and even suggest threshold values in the U.S. population for coronary artery disease. As the assessment stands, the risk characterization in section 6 of the draft report has little value as there is no way to link any interventions to possible health outcomes. It would be difficult and inappropriate to make a policy decision based on the uncertainty that the policy would have a health consequence from reducing arsenic and not a negative health impact from denying nutrients from rice.

II. RESPONSE TO CHARGE QUESTIONS

1. The risk assessment focuses on the risk associated with consumption of rice and rice products.

1.1. Have we adequately explained why FDA focused on these foods?

Yes, the selection for the focus and the explanation of the focus by the FDA are adequate.

1.2. If not, what additional information should we provide?

None.

2. Although we did not conduct a comprehensive literature search of all publications on all aspects of arsenic, we relied upon and cited other sources that have extensively reviewed the literature. Additionally, we included the newer research being published, especially on susceptible populations. With this in mind, did we include all pertinent recent literature?

The literature search was fairly comprehensive, and the presentation of the literature search was transparent. Absent is a 2014 study of the global cancer burden (lung, bladder, and skin) caused by arsenic in rice and food in general (Oberoi *et al., Cancer Epidemiol. Biomarkers Prev*., 23:1187-94, 2014). This risk estimate was made with the Morales 2001 data and has discussion that would support the findings of the current report.

3. Do you agree with the dose-response modeling approach, data selected, and assumptions that we used for assessing the lung and bladder cancer risk estimates?

The modeling approach and data selected for the cancer assessment are adequate, as is treatment of the Morales model and EPA assessment. The findings that the end results are within the confidence intervals of the two different models provides confidence that the estimates are reasonably consistent. However, as discussed, neither the current model nor the Morales model are able to assess the true risk of low-dose exposure to arsenic from food without a great amount of uncertainty. The extrapolation from the published dose-response relationships to the low dose range that causes the expansion of the confidence limit is a major limitation in providing an accurate assessment of the risk posed by arsenic intake from rice and rice products.

[Added from an earlier response from this reviewer. This paragraph was revised and appears in part in the General Impressions section] The limitation of no epidemiological studies linking normal food arsenic content to disease or adverse outcomes needs to be addressed. Also, more data are needed to understand the mitigating beneficial health effects of the other constituents in rice (e.g., folate, especially in enriched rice, niacin, and selenium) that may reduce risk from arsenic in rice. All of the data supporting the risk assessment comes from studies of health effects of arsenic in drinking water or where drinking water is the major concern. Aside from the issue of bioavailability that was addressed, it is not evident that arsenic in food poses an equivalent risk to arsenic in water, since water has few other mitigating constituents.

3.1. If not, what alternative modeling approaches should we consider? Specifically we are interested in comments on the model weighting used. For example, how much weight should be given to the different alternative models and what is your scientific rationale for the choices?

3.1.1. Additionally please comment on whether our use of the Morales model is consistent with the way it was used in developing the EPA 2001 Drinking Water Rule.

[The reviewer's comments are presented above under Question 3

3.2. Given the challenges of using epidemiology data for dose-response modeling and especially in this case, using data from non-U.S. population, please comment on whether FDA adequately justified the selected studies (Chen et al.). If not, what additional information should we provide in the report?

The Chen studies do add some strength to the modeling, but they are seriously limited in evaluating the lower end of the dose-response curves for bladder and more for lung cancer. The studies are well powered, but the urinary cancer risks are skewed by the relatively limited number of cases, and within a significant number of the cases, the arsenic levels are unknown. The lung cancer analysis suggests that the modeling is not statistically sound and that there appears to be a threshold for arsenic-induced lung cancers. This is not taken into account in the current modeling.

4. For prenatal and early life exposure, are there enough data of sufficient quality to develop a dose-response model and quantify the risk estimate for these two exposure periods (life stages)? If not, do you have suggestions to strengthen the text and to assist in the estimation of risk for adverse pregnancy and developmental outcomes?

The analyses in section 2.6 and discussion in section 6 are of insufficient quality to develop a dose-response model and quantify risk of non-cancer disease. There are not sufficient data available that clearly associate low-dose arsenic exposure in pregnancy to negative birth outcomes and cognitive problems in children. This is why the NRC committee placed these endpoints in Tier 2 (some epidemiological support, but not adequate dose-response relationships) and Tier 3 (weak epidemiological support, but a suggestion of causality) priorities.

The largest failing in the FDA assessment is the use of speculative qualitative assessment to generate a weight of evidence argument for a likely causal association between arsenic and pregnancy outcomes and then to suggest relevance to risk communication or suggested mitigation. It is difficult to see how any assessment can be made without establishing a reference or benchmark dose that can be used to determine whether the exposures from food, especially those estimated for exposure in rice, are sufficient to cause a risk of disease. There is no discussion of whether the dose response would present a threshold or no-effect level that is above the amount of arsenic in the diet, nor how dietary constituents and beneficial nutrients in rice (e.g., folate) would affect this threshold. The discussion in the second sentence of the paragraph at the top of page 85 is of no value and is meaningless, since there is no ability to determine whether this reduction in exposure would be of consequence in reducing real risk of disease. There are no data to support this supposition. The text even states this in section 2.6.1 where is says:

"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 makes difficult the determination of a Tolerable Daily Intake (TDI) for adverse effects during this life stage."

Without this idea of acceptable exposure it is unlikely that there is any means of improving the text to strengthen the risk estimate. The only way this can be achieved is to provide a full estimate of the risk after establishing the dose response for the non-cancer endpoints for exposures below 100 ppb. It is not evident why FDA attempted a qualitative assessment of the risks for birth outcomes or cognitive effects where there are few data when the NRC recommended focus on the Tier 1 endpoint of cardiovascular disease. There are sufficient highly powered prospective epidemiological studies that provide dose-response relationships for the cardiovascular disease effects of low-dose arsenic exposures, including a number of studies in the U.S. population.

5. Do you agree with our approach to exposure assessment, including the data and assumptions used. If not, what alternative approaches, data or assumptions should we consider?

The exposure assessment is adequate and fairly robust. A strength comes from breaking assessment into population exposure and serving exposure. Additional strength comes from combining the FDA and Consumer Reports studies of the arsenic content in rice and rice products, as well as adequate attention to separating inorganic from organic arsenical content.

6. Do you agree with the assumptions and scenarios we presented in the "What if?" section of the risk characterization?

For the most part, the "what if" interventions are adequate for reducing exposure, but the true benefits to reducing real risk are overstated. Section 6.2 lacks full risk communication and impact of the interventions suggested. Certainly reducing intake by 50% will result in a 50% reduction in exposure. However, there is no indication of the consequent reduction in cancer risk or incidence. There is no basis for making a statement of reduction in non-cancer endpoints, since no hazard quotient was established. Given the risk assessments above, these recommendations may have great economic impact and negative health impacts from reducing the nutrition gained from rice without any significant reduction in arsenic-promoted disease burden. Can a 50% reduction in the estimate of 2.4/million cancers to 1.2/million cancers be considered significant enough to warrant the intervention? The real risk estimates should be discussed here, although it would be apparent that there is very little lifetime risk of cancer from arsenic exposure in the 0-1 year (0.0002%) and a minimal gain from the estimated 6% reduction in this rate (down to 0.00019% risk) when arsenic in rice is eliminated from the diet (section 7.4 Key Finding: #4).

The FDA needs to provide data on the mitigating benefits of the other constituents in rice that decrease the negative health effects of arsenic. The assumption is that arsenic levels in rice present the same risk as in water, which is essentially true on the molecular level in the absence of considering cofounders. It is well known and stated in the document that nutritional status is a factor in determining disease susceptibility to arsenic exposures. Clearly, folate and selenium

status both contribute to mitigating arsenic effects, yet there is no discussion of the impact of the folate and selenium content of rice or rice products in shifting the dose response for arsenic cancers or non-cancer endpoints. There is no discussion of the impact of enriching rice and rice cereals with folate on reducing disease susceptibility. This may be an as effective "what if" intervention that reduces risk without imposing economic hardship, since rice and cereals are often already fortified.

6.1. Are there other scenarios that should be included? If so, please explain why and provide details about the additional scenarios for FDA to consider.

Many of the conclusions stated in Section 7.4 and the Executive Summary are supported by the data. However, they are communicated in a way that overstates the importance of the findings, especially for the risk estimates for the non-cancer estimates.

Specifically:
Page 3 (first bullet) and section 7.4: #4: It is admirable that the small risk of lung and bladder cancer caused by life time exposure to arsenic in rice is presented in the context of the general risk of lung and bladder cancer. However, in 7.4: #4, giving the percentages of lifetime risk for lung and bladder cancers for the general population out of context almost implies that arsenic generates 6.6% of lifetime risk when it is really 0.0039% lifetime risk of both cancers.

Section 7.4 #5 is very misleading in significance based on the spin of the data presentation which suggests that eliminating rice and grain product from the diet during infancy and childhood based on the arsenic content would reduce the lifetime risk of cancer 6% and 23% respectively. While this is a true statement, it hides the fact that this would have negligible impact on cancer risk (0.0002% to 0.00019% and 0.00091% to 0.0007% reductions in lifetime cancer risk respectively) at a potentially large negative health impact of denying the health benefits provided by eating rice and rice products.

Section 7.4 #6 Again the benefits of interventions are overstated by giving the percentages of negligible risk that would be reduced by lowering the arsenic content in rice to 50 ppb. Yes, this reduction in the limit, which would certainly pose economic hardship on the industry, would reduce the cancer risk by 70%. However, stating that this would reduce the cancer risk from 0.0039% to 0.0027% would convey the true health gain from this reduction.

Section 7.4: #8 In addition to understanding the impact of cooking techniques on the content of arsenic and nutrients in rice, it would be important to determine the impact of the nutrients on the health risk of the arsenic in rice.

7. Do you think the key findings and conclusions that we made are supported by the information provided in the risk assessment? If not, please explain what alternative findings and conclusions should be considered.

[The reviewer did not comment.]

8. Do you have any other comments or suggestions that are not elicited by 1-7?

See specific comments.

III. SPECIFIC OBSERVATIONS ON DRAFT ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DOCUMENT

Page	Paragraph/Line	Comment
2	First bullet of summary	The first bullet in the executive summary and much of the discussion of the relative risk of arsenic in brown and white rice needs to be rephrased. The implication of the bullet is that white rice is more hazardous than brown, which is not true. There is certainly more exposure to white rice, but the intrinsic risk of the arsenic dose in either type is the same. You would not want the reader to have more servings of brown rice to reduce the risk of disease from white rice
7-8	Last sentence	This is a misleading and essentially false statement. The USGS has numerous surveys of groundwater and aquifers in the United States that predict 8-12% of private wells that serve approximately 3 million people are contaminated with arsenic levels above the EPA MCL. A most recent USGS survey in Maine demonstrated that in some towns more than 30% of wells exceeded the MCL and some by up to 300 fold (3100 ppb; http://pubs.usgs.gov/sir/2010/5199/).
8	First paragraph, last sentence	Mention should be made of the recent, well powered, prospective epidemiological studies that link low-dose arsenic exposure to cardiovascular disease in the U.S.
24	First paragraph	The paragraphs that discuss the incident of the Japanese infants severely poisoned by acutely lethal levels of arsenic are not relevant and should be removed. Any connection between the neurological damage caused by these exposures to the disease promoting effects of low level exposures or long-term effects is highly speculative. There is no likely mechanistic similarity.
92	End of second paragraph	Same as previous
84-85	Section 6.1	Section 6.1 and the discussion of risk characterization of non-cancer health effects is inadequate and of little value. There is no means of providing a risk characterization (e.g., deriving a hazard quotient) without proper low-dose-response analysis. The weight of evidence is weak and not quantitative enough to support discussion of the impacts of reducing the low levels of exposure. The third paragraph of section 6.1 and table 6.1 are of no value to the discussion of risk of arsenic from rice consumption and should be removed. The statement first paragraph of page 85: *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."* is true, but has little meaning in understanding the reduction of real risk to the fetus that is provided. The one study that examined exposure to arsenic from rice in the U.S. had no disease outcomes associated with exposure. More importantly, there is a substantial body of evidence that has been cited in this RA and in the addendum that suggest a point of departure of $\geq$50 ppb. While correctly stated in the addendum that there are limitations that prevent defining the point of departure, the data are more compelling than this qualitative assessment. It would be difficult and inappropriate to make a policy decision based on the uncertainty that the policy would have a health consequence from reducing arsenic and not a negative health impact from denying nutrients from rice.

Page	Paragraph/Line	Comment
92	Third paragraph	"*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*." What is the basis for this statement and when do you expect to have the dose-response data that would be needed to support quantifying this risk?
96	Section 7.3 #2	These data are available for cardiovascular disease and should have been used to realistically estimate a non-cancer disease risk from the low amount of arsenic found in rice. Cardiovascular disease was recommended by the NRC 2013 as the highest priority non-cancer disease endpoint and it is not apparent why FDA chose two of the least substantiated endpoints to carry into a risk assessment. There is emerging data for cognitive effects in children with good animal data support, but the dose-response relationships are far from being established.

IV. SPECIFIC OBSERVATIONS ON DRAFT ADDENDUM TO FDA'S ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DATED MAY 2014

Page	Paragraph/Line	Comment
		No concerns, the addendum is well presented and conclusions are sound

V. SPECIFIC OBSERVATIONS ON FDA ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT CANCER MODEL

Tab	Steps taken within the tab	Comment
Dose response	Adjusting the dose to the expected exposure range	The dose-response model does not go down to the expected range of exposures from rice.

IV. Reviewer #4

Peer Review Comments on Arsenic in Rice and Rice Products Risk Assessment: Draft Report, Addendum, and Model

Reviewer #4

I. GENERAL IMPRESSIONS

Overall, I found this document very well written, logical, and easy to follow. I found the choice of the northeast Taiwan data as the basis of the risk assessment for lung and urinary tract cancer to be a reasonable decision. I also found the evaluation of the studies of neurodevelopment and adverse birth outcomes to be reasonably thorough and the decision not to use these data for quantitative risk assessment to be appropriate at this time. I had three major concerns. First, the risk estimates for bladder cancer seem to be much lower than those estimated by the U.S. EPA, and the reasons for this should be investigated and spelled out more clearly. A quantitative evaluation should be presented showing whether this difference is mostly due to the underlying data (northeast vs. southwest Taiwan data) or due to the modeling methods and assumptions. Second, the northeast Taiwan studies did not have lifetime exposure data on many people. They only had a single drinking water residential arsenic water concentration at the time of study enrollment. A quantitative evaluation of the potential impact of this on study results and risk estimates could be done and should be considered. Third, the risk estimates presented only include two of the many outcomes that have been linked to arsenic. For example, it seems fairly clear that in addition to cancer arsenic also causes cardiovascular disease. It should be noted that if other outcomes could be included to the models presented here, risk estimates would increase. My other concerns are mostly minor and are documented in the relevant sections of the documents. The risk assessment spreadsheets are a nice addition to this work, and these were very helpful is evaluating the impact of various factors on the model results.

[Note: This reviewer included comments within the body of the documents for both the Draft Arsenic in Rice and Rice Products Risk Assessment Document and the Draft Addendum to FDA's Arsenic in Rice and Rice Products Risk Assessment; refer to Attachments 1 and 2, respectively.]

II. RESPONSE TO CHARGE QUESTIONS

1. The risk assessment focuses on the risk associated with consumption of rice and rice products.

1.1. Have we adequately explained why FDA focused on these foods?

Yes, the FDA presents very solid evidence that arsenic levels in rice and rice products could be a concern.

1.2. If not, what additional information should we provide?

None

2. Although we did not conduct a comprehensive literature search of all publications on all

aspects of arsenic, we relied upon and cited other sources that have extensively reviewed the literature. Additionally, we included the newer research being published, especially on susceptible populations. With this in mind, did we include all pertinent recent literature?

Yes. A review of all studies on arsenic would be excessive and is not needed. My opinion is that FDA did a very good job at identifying the relevant studies. One concern was that studies regarding susceptibility were identified, but were not evaluated quantitatively. In other words, the degree to which some factors increase susceptibility was not evaluated. It's not clear that this is needed at this point, but it may be helpful if the increased risks in susceptible populations will be incorporated into interventions the FDA might eventually propose.

3. Do you agree with the dose-response modeling approach, data selected, and assumptions that we used for assessing the lung and bladder cancer risk estimates?

Yes, although see my comments regarding the Chile studies [Attachment 1]. A risk assessment using the Chile data might be useful in supporting the risk estimates presented here.

3.1. ***If not, what alternative modeling approaches should we consider? Specifically we are interested in comments on the model weighting used. For example, how much weight should be given to the different alternative models and what is your scientific rationale for the choices?***

Please see my comments in the document [Attachment 1]. Also, the reason for the actual weights for each of the three risk assessment models in the spreadsheets (3, 3, and 4 given to the Weibull, log-probit, and probit models) are not clear and should be explained. On visual inspection each of these three models seems to fit equally well. Since it would be hard to justify selecting one of these models over the others, has the FDA considered simply choosing the most conservative (cautious) one?

3.1.1. Additionally please comment on whether our use of the Morales model is consistent with the way it was used in developing the EPA 2001 Drinking Water Rule.

It appears appropriate and consistent.

3.2. Given the challenges of using epidemiology data for dose-response modeling and especially in this case, using data from non-U.S. population, please comment on whether FDA adequately justified the selected studies (Chen et al.). If not, what additional information should we provide in the report?

I believe the Chen *et al.,* 2010 studies are a reasonable choice for risk assessment given the good exposure range, good methods for ascertaining cancer cases, availability of data on potentially important confounders, and fairly reasonable exposure data. I have not seen any convincing evidence that arsenic-associated cancer risks will vary dramatically between the U.S. and Taiwan.

4. For prenatal and early life exposure, are there enough data of sufficient quality to develop a dose-response model and quantify the risk estimate for these two exposure periods (life stages)? If not, do you have suggestions to strengthen the text and to assist in the estimation of

risk for adverse pregnancy and developmental outcomes?
I agree with FDA's conclusion that there are not sufficient data to accurately quantify the risks for adverse pregnancy and developmental outcomes at this time. See my notes in the document for specific comments on this [Attachment 1].

5. Do you agree with our approach to exposure assessment, including the data and assumptions used. If not, what alternative approaches, data or assumptions should we consider?

Yes, I agree. The exposure assessment seems quite thorough and reasonable.

6. Do you agree with the assumptions and scenarios we presented in the "What if?" section of the risk characterization?

See my specific comments in the text [Attachment 1]. It would be helpful if FDA could provide a brief summary of why some of these "what if" scenarios are presented.

6.1 Are there other scenarios that should be included? If so, please explain why and provide details about the additional scenarios for FDA to consider.

None.

7. Do you think the key findings and conclusions that we made are supported by the information provided in the risk assessment? If not, please explain what alternative findings and conclusions should be considered.

I believe almost all of the key findings are supported. One major concern is that the bladder cancer risk estimates are much lower than those estimated by U.S. EPA. A more quantitative evaluation of the reasons for this difference should be presented.

8. Do you have any other comments or suggestions that are not elicited by 1-7?

No.

III. SPECIFIC OBSERVATIONS ON DRAFT ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DOCUMENT

Please see my comments in the documents [Attachment 1]

Page	Paragraph/Line	Comment
-	-	-

IV. SPECIFIC OBSERVATIONS ON DRAFT ADDENDUM TO FDA'S ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DATED MAY 2014

Please see my comments in the document [Attachment 2]

Page	Paragraph/Line	Comment
-	-	-

V. SPECIFIC OBSERVATIONS ON FDA ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT CANCER MODEL

[This reviewer did not provide any specific comments on the FDA Arsenic in Rice and Rice Products Risk Assessment Cancer Model.]

V. Reviewer #5

Peer Review Comments on Arsenic in Rice and Rice Products Risk Assessment:

Draft Report, Addendum, and Model

Reviewer #5

I. GENERAL IMPRESSIONS

The document provides a **quantitative** estimate of cancer occurrence from long-term exposure to inorganic arsenic in rice and rice products; and 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.

My perception is that the information that is provided is generally accurate, the presentation is clear with the risk assessment detailed according to the risk analysis framework including hazard identification, hazard characterization (dose-response) and exposure assessment. Some specific information throughout could be more clearly stated and these specific comments will be highlighted in my critique. The soundness of the conclusions is fair with some needed additional data to help the readers understand exactly where information has come from. There are questions about the model that was used that will be detailed in my critique.

II. RESPONSE TO CHARGE QUESTIONS

1. The risk assessment focuses on the risk associated with consumption of rice and rice products.
1.1. Have we adequately explained why FDA focused on these foods?

Yes, this was clear.

1.2. If not, what additional information should we provide?

NA

2. Although we did not conduct a comprehensive literature search of all publications on all aspects of arsenic, we relied upon and cited other sources that have extensively reviewed the literature. Additionally, we included the newer research being published, especially on susceptible populations. With this in mind, did we include all pertinent recent literature?

Yes, there are some citations that do not seem accurate. For example, it is important to highlight where citations are reviews versus using primary studies as documents such as this become used as references for many and this could provide information that is not accurate related to the primary data sources, for example. These are highlighted in the tables below.

3. Do you agree with the dose-response modeling approach, data selected, and assumptions that we used for assessing the lung and bladder cancer risk estimates?

The dose-response modeling has used a single study. The rationale for exclusion of some studies for the dose-response modeling is not clear. For example, were studies that used total arsenic in urine as a biomarker eliminated from inclusion? Why would this be the case as this is a well-accepted biomarker for arsenic exposure? Urine arsenic is in fact a better reflection of true exposure than using drinking water.

3.1. If not, what alternative modeling approaches should we consider? Specifically we are interested in comments on the model weighting used. For example, how much weight should be given to the different alternative models and what is your scientific rationale for the choices?

The modeling approaches and specifically weights as I can determine are stated as "Mean rice intakes were estimated using NHANES statistical weights developed for the 2-day dietary data, to correct for differences in population-response rates."

3.1.1. Additionally please comment on whether our use of the Morales model is consistent with the way it was used in developing the EPA 2001 Drinking Water Rule.

It seems to be in line with the DWR from 2001.

3.2. Given the challenges of using epidemiology data for dose-response modeling and especially in this case, using data from non-U.S. population, please comment on whether FDA adequately justified the selected studies (Chen et al.). If not, what additional information should we provide in the report?

More clarification would be helpful. For example, please state specifically in the document why the Chen *et al.* studies were used. Currently there is an explanation of why other studies were excluded but also please list then the inclusion criteria for Chen *et al.* Also this document needs to include a list of all studies that were included initially and all specific reasons explaining why those studies were not included.

4. For prenatal and early life exposure, are there enough data of sufficient quality to develop a dose-response model and quantify the risk estimate for these two exposure periods (life stages)? If not, do you have suggestions to strengthen the text and to assist in the estimation of risk for adverse pregnancy and developmental outcomes?

It seems there are data available and that the risk analysis has excluded studies such as those where total urinary arsenic was measured. Please explain why these were excluded specifically.

5. Do you agree with our approach to exposure assessment, including the data and assumptions used. If not, what alternative approaches, data or assumptions should we consider?

Yes.

6. Do you agree with the assumptions and scenarios we presented in the "What if?" section of the risk characterization?

Yes.

6.1. Are there other scenarios that should be included? If so, please explain why and provide details about the additional scenarios for FDA to consider.

NA

7. Do you think the key findings and conclusions that we made are supported by the information provided in the risk assessment? If not, please explain what alternative findings and conclusions should be considered.

Generally. Some suggestions are below, for example in stated finding #5 on page 117 "Reducing exposure to inorganic arsenic from rice grain and rice products reduces lifetime risk of cancer" – the information should be expanded. For example, provide a risk reduction statement for a reduction of rice consumed per week. This currently conveys that no rice consumption for children is the way to go.

8. Do you have any other comments or suggestions that are not elicited by 1-7?

NA

III. SPECIFIC OBSERVATIONS ON DRAFT ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DOCUMENT

Page	Paragraph/Line	Comment
6	First Paragraph	After "Descriptions of the search methods and selection criteria are provided in the text and appendices, as noted in each section of the report." **Please add which data are actually used in the risk assessment.**
12	First sentence	"studies, to break chromosomes and cause extensive damage to DNA in a variety of human tissues –**please comment on the concentrations required to break chromosomes**
16	Last paragraph	"There is evidence from several studies that increased cancer in adults may occur as a result of exposure during childhood (Tokar *et al.*, 2011; IARC, 2012)." **Please check the Tokar citation**
23	First paragraph	"Some studies used total arsenic in the urine as a biomarker of exposure." **To eliminate studies because individuals used total arsenic in urine seems inaccurate. Urine is the ideal biomarker for arsenic. It is actually unclear if this was used as an elimination factor for any studies-please clarify**
97	-	Key findings-the key findings that are summarized on page 97 need to cite the location within the risk assessment that are being referred to
42	First paragraph, line 14	"Of the remaining 13 studies, 4 were found to contain data appropriate for comparison with FDA data";-**which remaining 13? This number is not clear**

IV. SPECIFIC OBSERVATIONS ON DRAFT ADDENDUM TO FDA'S ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT DATED MAY 2014

Page	Paragraph/Line	Comment
11	Item 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." **Why is this? Please provide specific information on why the point of departure cannot be calculated with any of the new datasets.**
-	General comment	Missing references: **Prenatal Arsenic Exposure and the Epigenome: Identifying Sites of 5-methylcytosine Alterations that Predict Functional Changes in Gene Expression in Newborn Cord Blood and Subsequent Birth Outcomes**

V. SPECIFIC OBSERVATIONS ON FDA ARSENIC IN RICE AND RICE PRODUCTS RISK ASSESSMENT CANCER MODEL

Tab	Steps taken within the tab	Comment
-	-	No problems identified