FDA's Response to External Peer Review[1] on FDA's "Arsenic in Rice and Rice Products Risk Assessment: Draft Report" (July 2015), "Addendum to FDA's Arsenic in Rice and Rice Products Risk Assessment," and "Arsenic in Rice and Rice Products Risk Assessment Cancer Model"

February 19, 2016

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 work provides a comprehensive assessment that builds on and improves upon previously conducted FDA assessments and evaluations, and incorporates new information, where applicable.

The risk assessment was conducted by FDA scientists in consultation with arsenic experts and scientists from the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences and was revised in consideration of comments received during an OMB and interagency review. Three products were generated: the Arsenic in Rice and Rice Products Risk Assessment Report (version dated July 2015), the Addendum (update and discussion of literature from October 2013 through February 2015), and cancer risk-assessment model (accessed via a secured web-based application).

The peer review of the risk assessment documents and the cancer model evaluated FDA's approach, including selection of foods, supporting literature, data, assumptions, scenarios, and model design, as well as key findings and conclusions. For this peer review, five experts were independently selected by Versar Inc., to evaluate and provide written comments on: the Arsenic in Rice and Rice Products Risk Assessment Report (version dated July 2015), the Addendum, and the cancer risk-assessment model (i.e., the web-based application).

In Section II of this report, we list the charge questions given to the reviewers. In Section III of this report, we provide a summary of the peer reviewer comments, a description of changes made to the risk assessment report in response, where appropriate, and note areas where there was not concurrence among the peer reviewers.

[1] "Summary Report: External Peer Review of FDA's Arsenic in Rice and Rice Products Risk Assessment: Draft Report, Addendum, and Model." Versar, Inc., September 17, 2015.

Below are the names and affiliation of the peer reviewers:

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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 a 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. SUMMARY OF PEER REVIEWER COMMENTS AND FDA RESPONSE

General Impressions

Overall, the reviewers stated that the organization of the report was reasonable, and that the report was clear, well-written, logical and easy to follow. Reviewers provided various suggestions of where additional details could be added to aid the reader and support the report conclusions.

FDA Response: We appreciate the responses from the reviewers that the risk assessment and addendum, as a whole, were well-written and constructed. Overall, we agree with many of the points made by the reviewers regarding the need for additional clarification and we have added text for this purpose.

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

The reviewers agreed that the presentation was clear and the decision to focus on rice was reasonable and justified.

FDA Response: We appreciate the reviewers' comments regarding the clarity of the risk assessment and the focus of this report.

Question 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 reviewers agreed that the literature search was fairly comprehensive. A few reviewers suggested additional publications that could also be considered. One reviewer suggested that we should have included data on cardiovascular effects and diabetes. Reviewers also suggested that we more clearly indicate if the information reported was a primary study or from a review.

FDA Response: We thank the reviewers for their comments and suggestions on additional journal articles to consider. There appeared to be a general consensus that while not comprehensive, the literature presented was sufficient. The risk assessment considered studies up to October 2013 and the Addendum included journal articles from October 2013 – February 2015. In the Addendum our goal was to review newer studies for potential use in deriving a dose-response model for cancer and for two non-cancer endpoints, adverse pregnancy outcomes and neurodevelopmental effects in children.

We appreciate the suggested references. We continue to monitor the literature and consider whether any publications would likely lead us to conclusions that differ from those in the risk

assessment (that is, we use “stopping rules”). We also explained in more detail why we chose the two non-cancer endpoints that we did and added that we continue to work with EPA on additional modeling, including other adverse health effects, such as cardiovascular and diabetes. We also verified and corrected any incorrect citations.

Question 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?

There was general consensus among the reviewers with the dose-response modeling approach, while recognizing the limitations of the available data and methodology for dose-response model development. With regard to the limitations, one reviewer expressed concern about the use of the whole range of exposure, asked for more explanation of our assumptions in using these data, and asked how the dietary intake of arsenic was estimated. This same reviewer also commented on the potential use of a U-shaped dose-response, suggested restriction of our dose-response model to the first four data points, and questioned the estimation of cancer risk exposure during infancy and early childhood.

Another reviewer noted the uncertainty in risk estimates from extrapolation to low doses from high doses. A subsequent reviewer commented on the lack of statistical difference in lung and bladder cancer risk between 10 and 100 ppm exposure in the Chen et al., studies and that this is not consistent with linear models suggesting a possible threshold should be considered. One reviewer suggested that urine arsenic be used as a biomarker.

With regard to the data used for the dose-response modeling, one reviewer stated that the Taiwanese studies (Chen et al.) are “the only well-documented long-term data” while another reviewer suggested the Chile study for consideration as a possible additional data source to support our risk estimates. One reviewer indicated that the rationale for exclusion of some studies from the dose-response model was not clear.

Another reviewer commented that the Chen et al., studies only considered arsenic in drinking water and not rice, and it is not clear whether the Chen et al., studies took food sources of arsenic into account and the implications to the dose-response modeling.

FDA Response: We thank the reviewers for their substantive comments on our dose-response approach, data used, and assumptions for dose-response modeling.

Reviewers commented on uncertainty in the dose-response models. We acknowledge and characterize the uncertainty, including uncertainty introduced when extrapolating from high doses of the study data to the low dose exposure level of concern. We provide the uncertainty range in Table 7.1 and discuss in detail the sources of uncertainty in these estimates. The lack of

a statistically significant increase in risk at low doses in the Chen et al., studies is not inconsistent with the models we use to fit the data (linear and non-linear models). Actually, the sample size of these groups is too low to allow detection of a significant increase in the risk, which would be expected to be low. The small sample size in these groups (or, more precisely, the small number of cases) is translated in the dose-response model uncertainty, as part of the uncertainty in the data. While some authors suggest the presence of a threshold in the inorganic arsenic dose-response, we feel that there is still a lack of consensus on this issue in the arsenic scientific community.

While the idea of a U-shaped dose-response proposed by one of the reviewers is interesting, we feel further studies would be needed before it is used in an arsenic risk assessment modeling approach. Similarly, removing one data point out of five, as suggested by a reviewer, without strong supporting evidence would be highly criticized.

With regard to the question about how we estimated cancer risk during infancy and early childhood, we did consider the higher exposure (per body weight) during infancy and early childhood. However, there are insufficient data at this time to consider or quantify a potential higher susceptibility for this life stage.

Reviewers commented on the potential limitations of the Chen et al. studies for the purposes of risk assessment and questioned why other studies were excluded or not chosen. In general, all epidemiology studies have strengths and limitations. Epidemiology researchers choose their analysis methods based on the available data and resources. Given the variation in the methods and data utilized in different studies, most studies will have some limitations when used to derive a dose-response model. Among the published studies available at the time that the risk assessment was conducted, the Chen et al. studies had notable strengths that led us as well as Joint FAO/WHO Expert Committee on Food Additives (JECFA) and EPA to select these studies for the risk assessment.

The Chen et al. studies were selected by the JECFA committee as the pivotal study for bladder cancer (including all observed urinary tract cancers) and lung cancer. Regarding why other epidemiology studies were excluded, we considered different studies and decided that the Chen et al. studies were the best choice for our purpose, since they were well-designed, well-executed large prospective cohort studies. We are collaborating with EPA to explore additional methodological approaches such as meta-analysis of multiple studies with different study designs.

In regards to the comment about using urinary arsenic measurements, we agree that urinary arsenic measures are useful biomarkers for recent total arsenic exposure but not for chronic

exposure. We did not exclude these studies and our reasons for choosing the Chen et al. studies are outlined below.

In answer to the question about whether the Chen et al. studies took food sources of arsenic into account or not, they did not. However, we did consider inorganic arsenic from the diet using estimates from WHO/JECFA. WHO/JECFA provided estimates of the inorganic arsenic intake in the Taiwanese population, to be added to the dose from water intake, when using the Chen et al. data. We have edited the text to provide more details on the way we estimated the inorganic arsenic intake from the Chen et al. studies.

Question 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?

Three reviewers had no comments on the model weighting. One reviewer commented that the reasons for the weights were not entirely clear and should be explained.

One reviewer expressed a number of concerns with the use of the Chen et al. studies and how these data were used in the risk assessment e.g. transformation of water concentrations into doses, clarification of assumptions, estimation of dietary intake of arsenic, extrapolation of low doses, comparison with other risk assessments needs further explanation, and a comparison with more recently published literature should be considered. The same reviewer suggested better and more explanation was needed about choices made regarding the data in these studies.

FDA Response: Appendix 9.4 of the risk assessment report provides full details on model weighting. The FDA model is consistent with the NRC suggestion to fit linear and non-linear models to observed data (NRC, 2013, Box 7). Although NRC provided an example that used a single dose-response model form, eight alternative models were considered for the FDA dose-response derivation, and these eight models were used to represent model uncertainty. The eight alternative models used to characterize the shape of the dose-response relationship were employed to estimate the risk below the range of statistically significant differences among groups, as was recommended by NRC (2013). Model uncertainty has a large impact on the final estimates. Rather than picking a single dose-response model, we preferred to consider the uncertainty around these models (i.e., model uncertainty).

We addressed questions and concerns regarding the use of the Chen et al. studies in our response above and under the response to Question 3.2.

Question 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.

Four reviewers agreed that the use of the Morales model is useful and it appears to be consistent with the EPA 2001 Drinking Water Rule. One reviewer expressed concerns which have been addressed in part in the response to Question 3.1 above. One of the four reviewers that agreed with our use of the Morales model also noted that the Chen et al. studies suggested that there may be a threshold at arsenic concentrations below 50 ppm.

FDA Response: We appreciate the reviewer comments with regard to the Morales model. The Morales dose-response is included in the uncertainty range of the dose-response used in this risk assessment. We addressed the issue of whether the Chen et al. studies indicate that there may be a threshold at low doses above in our answer to Question 3.

Question 3.2: Given the challenges of using epidemiology data for dose-response modeling and especially in this case, using data from a 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?

All of the reviewers identified limitations in the Chen et al. studies used for the dose-response modeling. Many of these limitations have been addressed by previous comments and our responses to those comments. One reviewer questioned whether the Chen et al. studies considered arsenic from rice and whether it is possible that the Taiwanese population adapted to high levels of arsenic as had been suggested in a Chilean population. One reviewer thought that the follow-up time was too short. Another reviewer noted the limitations of these studies at low doses. More clarification was also suggested as to our reasons for using the Chen et al. studies.

FDA Response: We acknowledge that the Chen et al. studies and all similar studies have limitations for use in dose-response modeling and we have discussed these limitations in the risk assessment report. The Chen et al. studies contain well-documented, long-term data for lung and urinary tract cancer dose-response modeling. These studies were selected by the JECFA committee as the pivotal studies for bladder cancer (including all observed urinary tract cancers) and lung cancer risk assessment. FDA also considered the Chen et al. studies to be best suited for inorganic arsenic dose-response modeling, because statistically significant changes in disease rates were observed at two levels of exposure and because lung and bladder cancer are more serious effects, compared with other health effects (e.g., arsenic-induced skin cancer). We did consider inorganic arsenic from the diet using estimates from WHO/JECFA. WHO/JECFA provided estimates of the inorganic arsenic intake in the Taiwanese population, to be added to the dose from water intake when studying the data from the Chen et al. studies. The reviewer's observation regarding the Chilean population and adaptation to high arsenic levels is interesting and possibly could be applied to the Taiwanese population. However, we have not edited the text at this time to discuss this possibility. We did consider, in the evaluation of the uncertainty, the

impact of a limited number of cases and the uncertainty around arsenic doses in the development of the current risk assessment.

Question 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?

Three reviewers agree that data are not sufficient to develop a dose-response model at this time for adverse pregnancy and developmental outcomes. Two reviewers believe that there are some available data to develop a dose-response model. One of these reviewers acknowledges that there are limitations but believes it would be possible to determine some quantitative risk estimates. The other believes there are data using urinary total arsenic. One reviewer mentioned shortcomings of the Quansah et al., 2015, meta-analysis of the pregnancy studies. One reviewer asked why we did not evaluate the combined exposure of cadmium and arsenic effects on fetal development. One reviewer provided suggested edits and clarifications within the document.

FDA Response: We appreciate the comments and have made edits in the text to address some of the responses to provide further clarification. The disagreement among reviewers about the strength of the data for developing a dose-response model supports our conclusion that there is currently no scientific consensus that a defensible scientifically-supportable level for these adverse effects can be developed at this time. FDA continues to monitor the scientific literature in consultation with our federal partners for any new data that may allow a quantitative estimate.

One reviewer mistakenly thought we were using a weight-of-the-evidence approach. This is incorrect and we edited the text to more clearly indicate that we incorporated the elements of systematic review into our literature evaluation. Using this approach is more transparent and resulted in less bias than other approaches.

We discuss the meta-analysis of the pregnancy studies (Quansah *et al*., 2015) in the addendum. We agreed with the conclusion of the authors of that paper that there was too much dissimilarity between the various studies to have strong confidence in the results of that meta-analysis for use as a point of departure for developing a risk level.

The suggestion by one reviewer to consider the combined effects of cadmium and arsenic on fetal development is an interesting question. However, the interaction of arsenic and cadmium is out of scope for this risk assessment and currently there are insufficient data to conduct a risk assessment on this issue.

We agree that there are other non-cancer areas of concern for the toxicity of inorganic arsenic, such as cardiovascular disease or diabetes. We focused on adverse pregnancy outcomes and neurodevelopmental endpoints for three reasons. The first is because there is strong scientific evidence that pregnancy and early childhood are "windows of susceptibility" to the toxic effects of metals. The second reason is that arsenic readily crosses the placenta. The third reason is because FDA's sampling of infant rice cereal found high levels of inorganic arsenic in this product.

Scientific articles with urinary arsenic levels were not eliminated because they used this measurement of arsenic exposure. If they were not included, they did not meet one of the exclusion factors listed in Section 2.6 of the risk assessment report.

Question 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?

All of the reviewers agreed with our approach and noted that it was adequate and reasonable. One reviewer expressed some concern that the consumption estimates did not specifically include estimated current or future consumption of rice for certain ethnic or cultural subpopulations (such as consumers of Hispanic or Asian origin).

FDA Response: We appreciate the comments and the general agreement with our approach. The consumption data used in the risk model considered the U.S. population as a whole (including ethnic subpopulations). In addition to providing risk estimates on the basis of per capita we also provided risk estimates on a per serving basis. One reviewer made comments regarding the exposure assessment directly in the risk assessment. Clarification of the text was suggested and we edited the text to address these concerns. This same reviewer also asked that we provide rice intakes/inorganic arsenic exposures on an absolute basis (i.e., not divided by kg bw) in the text. We provide this information in an appendix and therefore did not alter the risk assessment text to include the absolute intakes.

We considered the reviewer comment that per capita rice consumption (and inorganic arsenic exposure from rice consumption) is likely to increase if there is greater representation of individuals of Hispanic and Asian origin in the general population in the future. Unfortunately, we do not have data sufficient to allow development of scenarios based on possible or projected changing demographics. However, we do provide the rice inorganic arsenic concentration standard error of the mean (SEMs) and ranges in Tables 4.2, 4.3, and 4.5 to provide perspective on variability. Additionally, we address the impact of higher frequency of exposure on cancer risk in the "what-if" scenarios.

Question 6: Do you agree with the assumptions and scenarios we presented in the "what-if" section of the risk characterization?

All of the reviewers agreed that our "what-if" scenarios were informative. One reviewer asked that the basis for the scenarios presented be better explained with regard to the reason for their selection. Another reviewer stated that the benefits of reducing real risk are overstated and suggested that we provide data on benefits of rice.

FDA Response: We thank the reviewers for their comments. Although we recognize that there are benefits to eating rice, we did not conduct a risk-benefit analysis due to insufficient data. Therefore, accounting for the nutritional constituents in rice, some obtained through fortification such as folate or iron, is outside the scope of this risk assessment; such attributes of rice would be considered in risk management or mitigation actions. In our cited research on different cooking methods for rice, we considered the impact of the cooking methods on the presence of inorganic arsenic and certain nutrients.

We agree that we cannot quantitate the degree of risk reduction from the non-cancer endpoints that would result from a 50% decrease in exposure. These "what-if" scenarios were added not to quantitate risk or to dictate risk mitigation strategies but rather they were "thought-provokers" for our risk management team. We disagree with the reviewer who suggested that the risk assessment should provide consumer advice; the purpose of the risk assessment is to provide information to risk managers for decision-making, which might include consumer advice.

Question 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.

No additional "what-if" scenarios were suggested by four of the reviewers. One reviewer suggested that the additive risk of arsenic in water and arsenic in rice should be considered. Another reviewer commented on the topics addressed in Question 7.

FDA Response: We thank the reviewers for considering the "what-if" scenarios. We did not conduct a scenario that considers the additive risk of arsenic in water. We have focused on risks from exposure to inorganic arsenic from rice and rice products without consideration of the additional exposure to inorganic arsenic from other sources, including the water used to cook rice. This risk assessment was not intended to consider total dietary burden or exposure beyond that of rice and rice products.

Question 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.

There was general agreement that the key findings and conclusions were supported by the information in the risk assessment. One reviewer provided a list of issues/concerns regarding several key findings summarized in the conclusions which we respond to below. Another reviewer provided some additional comments that provided context for lifetime cancer risk percentages under Key Finding #4.

FDA Response: Regarding the suggestion that we provide the ranges of inorganic arsenic concentrations in Section 7.4, Key Findings, point #2 -- we do agree that the mean is as important as the range and we provide this information in the appropriate sections of the report and do not agree that this information needs to be repeated in the summary/conclusion section. Regarding the suggestion to include something about the related health risks in Section 7.4, Key Findings, point #3, which provides a description of the levels of MMA and DMA from FDA's survey study -- we provide a discussion of the adverse health effects from exposure to arsenic in Sections 4.7 and 7.1 of the report and do not agree that further elaboration is needed in the summary conclusion section. We are closely following emerging science on possible toxicity of organic arsenic species. Furthermore, as indicated in the Key Findings section, we measured very little MMA in rice. There were several comments regarding the summary of the results of the FDA cancer models (point #4, Section 7.4 of the risk assessment). First, while we agree there can be uncertainty associated with any risk model, we do not agree that there is any information to indicate that the FDA cancer models underestimate the risk. We do agree that the risk can be higher for some consumers. Therefore we included scenarios to evaluate the risk for infants, children, and high consumers of rice (see scenarios). Second, as suggested, we edited the text to include information on relative intake (per capita basis and per serving basis) with the corresponding predicted cancer risk. Detailed information is provided in the report and appendices. Third, we believe that providing the background number of lung and bladder cancer rates for all causes including smoking provides important context for the predicted cancer cases attributed to consumption of rice. We were not able to find lung and bladder cancer rates specific for diet-related cancer risks so did not include that suggested information. As suggested, we included the uncertainty range for the average reported risk estimates. Whether the average risk per capita is considered "acceptable" or not is a decision to be made by risk managers (not risk assessors) and would likely take into account a variety of factors. We agree that arsenic may cause or be associated with many types of adverse health effects and we describe in the report why we chose to focus on certain adverse health effects. This information is provided in earlier sections of the report. We do not agree with the suggestion that we remove the scenario that discusses eliminating rice and rice products from the diets of infants and children. This is a reasonable scenario because it is possible to substitute other infant cereals for infant rice cereal. For example, there are oat, wheat, and barley infant cereals that are fortified to provide key nutrients to infants and all are much lower in inorganic arsenic content. Additionally, infants can consume fruit and vegetable baby products. Furthermore, parents of children requiring special

diets (e.g., milk- and/or gluten-free) should discuss alternatives with their physician. Contrary to the reviewer statement, we believe that establishing a standard for inorganic arsenic in rice would remove from the marketplace product with higher levels of inorganic arsenic. Through sourcing and testing, it is possible to achieve limits for products in the food supply. The purpose of the risk assessment is to provide information essential for making science-based, risk management decisions, not to determine whether a standard should be set. Therefore, we do not agree with the suggestion that the scenario which measures the impact of various mandatory or voluntary limits should be removed from the risk assessment. Regarding the comments on Key Findings, point #7 which summarizes the scenarios for the impact on risk from changes in infant cereal consumption – while we agree that reducing arsenic in beverages would reduce the risk, that is not purpose of this risk assessment scenario. We do not agree with the statement that there are no suitable alternative, low-arsenic containing foods, therefore we believe this scenario presents a feasible option for parents of young children, based on available products in the marketplace, and is appropriate to include in the risk assessment. We agree that cooking practices to reduce arsenic is important information and we provided details of published research, including a recent study by FDA scientists, in Section 5.3 of the report. We have not expanded the text for Key Findings point #8 to describe cooking practices because we do not believe this level of detail is needed in the summary conclusion section. Regarding the comment about Key Findings point #9, we agree and edited the text to describe the impact to reduce cancer risk from reducing the amount consumed per eating occasion and frequency of consumption instead of describing the impact to increase cancer risk from increasing the amount consumed and frequency of consumption.

Regarding the reviewer comment concerning U.S. EPA estimates for bladder cancer, as noted above, FDA is collaborating with EPA as it refines cancer estimates. Regarding the reviewer comment for Key Findings point #5, we provide information about changes in risk associated with changes in frequency of consumption in the report and this information is also summarized in Key Findings point #7.

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

One reviewer suggested ways to limit arsenic in rice such as water management, limiting where rice can be grown to low arsenic regions, and selection of cultivars that accumulate less arsenic. One reviewer requested that we include market-share data by geographic regions. One reviewer suggested changing units from ppb/ppm notation to µg/mg per kg or liter.

FDA Response: We are aware of the ongoing agricultural research to develop ways to mitigate arsenic in rice such as water management and plant breeding, and interest in understanding whether and to what extent there is predictable variability among geographic regions that can be factored into risk management decisions. Considering these types of mitigation options and

evaluating the impact on predicted risk will be an important next step for public and private risk managers, but it is beyond the scope of this risk assessment. Lastly, we do not agree that the ppb/ppm system is out-of-date as the reviewer indicated and did not make this suggested change to the units.

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

Specific comments and concerns were addressed and text changes were made to the report. We appreciate the suggested literature additions. The post-peer review version of the risk assessment includes a literature review of studies published up to February 2015. We continue to monitor the literature and consider whether any publications would likely lead us to conclusions that differ from those in the risk assessment (that is, we use "stopping rules").

One reviewer suggested the addition of information on metabolism and pharmacokinetics of arsenic in rats and mice in the Hazard Identification section of the report. We are aware that arsenic has been shown to be both embryotoxic and teratogenic in experimental animals that are given high doses. We are also aware of studies in mice where exposure during the embryonic period causes an increase in the number and timing of tumors in adult life. However, because the kinetics and toxicity of arsenic varies greatly between animal species and between animals and humans, the extrapolation of these data to humans is difficult.

One reviewer asked if the differences between the FDA model and the EPA model could be defined quantitatively e.g. what percentage of the difference is due to differences in the risk seen in the different underlying studies (NE vs. SW Taiwan) versus what percentage is due to differences in modeling and assumption. As can be seen in Tables 3.5 and 3.6 in Section 3, the number of predicted cases per million for bladder and lung cancer with the EPA model and the FDA model are close. More importantly, the confidence interval of the FDA model estimate includes that of the EPA model estimates. Overall, the estimates from the current FDA model and the 2001 EPA model are quite similar. The FDA model included and considered more sources of uncertainty.

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

Overall, peer reviewers described the conclusions in the addendum as clear, sound and comprehensive. Two reviewers suggested that we add additional references to the addendum. As stated previously, we continue to monitor the literature for additional studies that might augment or further our risk assessment conclusions, but have not added them to the addendum at this time.

One reviewer questioned why we stated that new data were not sufficient to develop a point of departure for adverse pregnancy outcomes. We assume the reviewer is referring to the meta-analysis of the pregnancy studies (Quansah *et al*., 2015) which we discuss in the addendum. We agreed with the conclusion of the authors of that paper that there was too much dissimilarity between the various studies to have strong confidence in the results. We addressed this comment in the addendum by expanding the justification of why we did not believe these new data are sufficient to develop a point of departure for adverse pregnancy outcomes.

Finally, reviewers suggested additional clarification of studies described within the addendum including information related to exposure, dose-effect relationships, and study strengths and limitations. We considered the reviewers' suggestions and added clarification throughout the addendum where appropriate.

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

One reviewer requested additional information be included: (1) further breakdown the types of rice into geographical regions; (2) break out the risk for the Asian population; and (3) provide predictions for future years assuming that the percentage of Hispanic and Asian populations will increase. We have addressed these concerns above. There is insufficient information and data to calculate predicted risk for rice types by geographical region, for the Asian population, and for possible future demographics.

One reviewer suggested that we adjust the dose to expected exposure range for rice. The cancer model integrates the dose-response and exposure assessment to predict risk based on expected levels of inorganic arsenic in rice.