Faculdade de Saúde Pública

Universidade de São Paulo

Avaliação de risco à saúde humana devido a presença de arsênio e outros elementos em arroz no Brasil

Michele Cavalcanti Toledo

Tese apresentada ao Programa de Pós-graduação em Saúde Pública para obtenção do título de Doutor em Ciências

Linha de pesquisa: Saúde Ambiental, modos de vida e sustentabilidade.

Sublinha: Avaliação de exposição e riscos por agentes ambientais

Orientadora: Profa. Dra. Adelaide Cassia Nardocci

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Dedico este trabalho a todas e todos os cientistas brasileiros, que seguem na luta em tempos sombrios, buscando um mundo mais saudável para todos.

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“Hey you

Don’t tell me there is no hope at all

Together we stand, divided we fall”

Hey you – Roger Waters

RESUMO

Toledo, M. C. Avaliação de risco à saúde humana devido a presença de arsênio e outros elementos em arroz no Brasil. 2021. Tese – Faculdade de Saúde Pública da USP; 2021.

Introdução: Arroz pode ser a principal fonte de exposição a arsênio inorgânico (iAs), que é carcinogênico e está associado a diversos efeitos não-carcinogênicos. Produtos feitos de arroz, como cereais infantis, e água para consumo podem ser importantes fontes de exposição a iAs. Embora o arroz seja um componente básico da dieta da população brasileira, há poucos estudos avaliando os riscos à saúde decorrentes da exposição ao iAs. **Objetivo:** Avaliar o risco da exposição a iAs e/ou outros elementos tóxicos e essenciais em arroz integral, arroz branco, cereais infantis, e água potável no Brasil, e identificar possíveis medidas para mitigar o risco. **Método:** O incremento de risco de câncer no tempo de vida (ILCR), o risco não-carcinogênico (HQ) e o *hazard Index* (HI) foram estimados através de análise probabilística com simulações de Monte Carlo. A concentração de elementos em arroz e cereais infantis foi obtida de pesquisas realizadas no Brasil, e a concentração de arsênio em água provém do monitoramento nacional de vigilância da qualidade da água. **Resultados e discussão:** O ILCR médio para exposição a iAs em arroz branco foi 1.3×10^{-04}, arroz integral 5.4×10^{-06}, e para exposição a chumbo (Pb) em arroz integral foi 2.5×10^{-8}. O HQ para arroz foi estimado abaixo de 1 para todos os elementos, assim como o HI, sugerindo que efeitos não carcinogênicos não são esperados. O ILCR médio decorrente da exposição a iAs em água foi 6.5×10^{-05}, acima do limite de 1×10^{-5}, e o HQ foi inferior a 1. Cereais infantis feitos de arroz foram o tipo de cereal com maior ILCR (4.0×10^{-5}) e com mais elementos com HQ acima de 1. Todos os cereais infantis apresentaram HQ acima de 1 para ao menos um elemento. Cadmio foi o elemento tóxico mais significativo, e zinco o elemento essencial mais relevante. Estimou-se que através de ações de mitigação o risco carcinogênico devido ao consumo de arroz poderia ser reduzido em até 68%, e para cereais infantis em 24%. O ILCR para arroz foi considerado elevado, ainda que as concentrações de iAs estejam dentro dos limites permitidos. O risco para arroz integral foi menor que para arroz branco, devido à baixa concentração de iAs nas amostras avaliadas, e as possíveis razões para isto foram exploradas, como o local do cultivo, práticas agrícolas e o tipo de cultivar de arroz. O risco carcinogênico e não-carcinogênico referente a exposição a Pb foi considerado baixo, entretanto nenhum nível de exposição a este elemento é considerado seguro. **Conclusões:** O ILCR para consumo de arroz, cereal infantil e água foi considerado elevado. O risco não-carcinogênico foi considerado elevado apenas para cereais infantis, incluindo elementos tóxicos e essenciais, e cereais infantis feitos de arroz apresentaram risco mais significativo. O consumo de água representou um menor risco carcinogênico, entretanto considerado não tolerável. Com o suporte de políticas públicas, medidas para reduzir os riscos relativos ao consumo de arroz e cereais infantis poderiam ter um impacto positivo para a saúde pública no Brasil.

Descritores: Método de Monte Carlo; Chumbo; Alimentação Básica; Alimentação; Avaliação de Riscos e Mitigação; Alimentos Infantis; Água potável;

ABSTRACT

Toledo, M. C. [Risk assessment from exposure to arsenic and other elements in rice from Brazil]. 2021. Thesis – Faculdade de Saúde Pública da USP; 2021. Portuguese.

Introduction: Rice can be the main source of exposure to inorganic arsenic (iAs), which is classified as carcinogenic and is also associated with non-cancer effects. Rice products, such as infant cereals, and drinking water are also important sources of exposure to iAs. Although rice is a staple food in Brazil, there have been few studies about the health risks for the Brazilian population. **Objective:** The objective of this study was to assess the risks of exposure to iAs and other toxic and essential elements from brown rice, white rice (only iAs), infant cereal (made of rice and different raw materials), and drinking water (only iAs) in Brazil, and to identify possible measures to mitigate those risks. **Method:** The incremental lifetime cancer risk (ILCR) and the non-cancer risk, or hazard quotient (HQ), and hazard index (HI) were calculated. A probabilistic analysis was performed with Monte Carlo simulation. **Results and discussion:** The mean ILCR was 1.3×10^{-04} for exposure to iAs in white rice and 5.4×10^{-06} for brown rice, and for exposure to Pb it was 2.5×10^{-8} for brown rice. The HQ was under 1 for all elements in brown rice, as the HI, suggesting that health effects are unlikely. The mean ILCR for exposure to iAs from drinking water was 6.5×10^{-05}, above the tolerable value of 1×10^{-5} recommended by the World Health Organization, and the HQ was below 1. Rice cereal was the kind of infant cereal with highest ILCR (4.0×10^{-5}) and with more elements with HQ above 1. All the infant cereals had an HQ above 1 for at least one element. Cd was the non-essential element more significative in this scenario, and Zn was the essential element more relevant. Various mitigation measures discussed in this dissertation are estimated to reduce the risk from rice consumption by 68%, and from infant cereal by 24%. The ILCR for white and brown rice was high, even though the iAs concentration in rice is below the maximum contaminant level. The risk for brown rice consumption was lower because the iAs concentrations were low in the brown rice samples evaluated, which possible reasons were explored, such as the location of cultivation, agricultural practices and the kind of rice cultivar. The estimated cancer and non-cancer risk from exposure to Pb is low, however no exposure to this element from diet is considered safe. **Conclusions:** The ILCR for rice, infant cereal and water consumption was considered high. The non-cancer risk was not tolerable only for infant cereal, including essential and non-essential elements, and rice cereal showed to be more concerning. Water consumption represents a small part of the risk for adults, although it was estimated to be not tolerable. With the support of public policies, measures to reduce these risks from rice and infant cereal would have a positive impact on public health in Brazil.

Descriptors: Monte Carlo Method; Lead; Staple food; Diet; Risk Evaluation and Mitigation; Child; Infant food; Drinking water.

SIGLAS E ABREVIATURAS

ADD - Average Daily Dose

AIC - Akaike information criterion

ANVISA – Agênncia Nacional de Vigilância Sanitária

AQR – Avaliação Quantitativa de Riscos

As(III) – Arsenito

As(V) – Arsenato

AT – Tempo médio da exposição

BNMH – Brazilian National Ministry of Health

DMA – Dimethylarsinic acid

EF – Frequência da exposição

EFSA – European Food Safety Authority

EPA – United States Environmental Protection Agency

EUA – Estados Unidos da América

FAO – Food and Agruculture Organization

FDA – United States Food and Drug Administration

HI – Harzard Idex

HQ – Hazard Quotient

IARC – International Agency for Research on Cancer

iAs – Inorganic arsenic

IBGE – Instituto Brasileiro de Geografia e Estatísticas

ILCR – Incremento de risco de câncer no tempo de vida

IR – Taxa de ingestão

LOD – Limite de detecção

LOQ – Limite de quantificação

LT – Tempo de vida

MCL – Maximum contaminant level

MMA – Monomethylarsonic acid

ONU – Organização das Nações Unidas

OMS – Organização Mundial da Saúde

PTWI – Provisional tolerable weekly intake

SD – Standard deviation

SF – Fator de carcinogenicidade

SISAGUA – Sistema de Informação de Vigilância da Qualidade da Água para o Consumo Humano

USA – United States of America

WHO – World Health Organization

SUMÁRIO

1. APRESENTAÇÃO

Esta tese de doutorado está apresentada na forma de artigo, de modo que a seção Resultados e Discussão é composta por três artigos escritos como produto desta pesquisa, que foram preparados para submissão para revistas científicas.

Por questões de direitos autorais, os manuscritos não serão disponibilizados ao público nesta tese, mas os mesmos podem ser acessados por meio das revistas em que estarão publicados.

2. INTRODUÇÃO

É comum que plantas absorvam elementos químicos do solo e água utilizada para irrigação, alguns dos quais têm sido reconhecidos como tóxicos para organismos vivos, incluindo seres humanos, mesmo em baixas concentrações. Tais elementos podem ter ocorrência natural, devido a composição de rochas e solos, ou podem ter fontes antrópicas, como indústrias, mineração, dentre outros. Destacam-se o arsênio, o chumbo, o cádmio, o cromo, e o mercúrio. Desta forma, a incorporação destes elementos na cadeia alimentar tem ganhado destaque nas pesquisas atuais sobre expossoma (MILLER; JONES, 2014).

Algumas das plantas que têm esta característica de acumular concentrações traço de elementos tóxicos provindos do solo e água são alimentos amplamente consumidos atualmente. Durante seu cultivo, tais elementos podem se acumular nos frutos, folhas, caule e/ou raiz do vegetal, e podem representar riscos para saúde humana (ANTOINE et al., 2017; AL-SALEH; ABDULJABBAR, 2017; FLEURY et al., 2017).

O arroz (*Oryza sativa*), um cereal amplamente consumido ao redor do mundo, tem sido reconhecido por sua capacidade de armazenar arsênio inorgânico nos grãos, o que representa riscos à saúde de populações que o consomem diariamente. A planta absorve uma quantidade relativamente elevada de arsênio, o que é resultado de uma combinação das características fisiológicas da planta, e de seu método de cultivo. O plantio, que ocorre geralmente em áreas alagadas, em condição anaeróbia, resulta em um meio redutor, onde bactérias anaeróbias reduzem arsenato [As(V)] em arsenito [As(III)], uma forma mais móvel e biodisponível para a planta. (Joint FAO/WHO, 2017; Zhao, McGrath e Meharg, 2010).

A absorção de arsenito pela planta pode ser mais significativa, mas podem também ser encontrados no grão de arroz arsenato, além das formas orgânicas do arsênio (ácido monometilarsonico e ácido dimetilarsinico), menos abundantes e cuja toxicidade conhecida neste momento aparenta ser menos relevante (U.S. FDA, 2016; Zhao, McGrath e Meharg, 2010).

A exposição ao arsênio inorgânico está associada a efeitos adversos à saúde descritos como danos ao sistema cardiovascular e dérmico (U.S. EPA, 1995). São ainda observados danos neurológicos, diabetes, problemas cardiovasculares e no sistema reprodutivo (HONG; SONG; CHUNG, 2014). É também considerado carcinogênico pela *International Agency for Research on Cancer* (IARC), que avalia substâncias e compostos químicos quanto ao seu potencial carcinogênico, de modo que o arsênio inorgânico foi classificado como Grupo 1, onde se tem elevada confiança de que o agente químico é carcinogênico para humanos (WHO, 2012). A exposição ao arsênio inorgânico éassociad a a câncer de pele e do sistema respiratório (U.S. EPA, 1995). Há ainda evidências de câncer de bexiga, rim, fígado, próstata e leucemia (HONG; SONG; CHUNG, 2014).

Além das altas concentrações de arsênio, especialmente arsênio inorgânico (iAs), o elevado consumo de arroz contribui significativamente para um cenário de risco. Segundo dados da *Food and Agriculture Organization of the United Nations* (FAO), a ingestão de arroz responde por 30% do suporte energético e 20% da ingestão de proteína em todo mundo (FAO, 2004). O arroz compõe substancialmente a dieta da população mundial, sendo que cerca de metade da população o tem como alimento básico (GROSS; ZHAO, 2014).

Na Europa, o arroz foi considerado pelo *European Food Safety Authority* (EFSA) a maior fonte de iAs para a população (EFSA, 2014). HONG et al. (2014) fizeram uma revisão da literatura sobre arsênio e identificaram estudos que encontraram consideráveis concentrações de arsênio no corpo humano.

No Brasil, a produção de arroz e outros grãos têm aumentado substancialmente. Em 1970, a produção de arroz, feijão, milho, soja e trigo somavam 27,3 toneladas. Em 2016, este valor passou para 204 toneladas, representando uma variação de 649,33% (EMBRAPA, 2017). Estima-se que a média de consumo de arroz pelo brasileiro seja de 140,9 g por dia (IBGE, 2020). O consumo do grão é difundido no país como um componente básico da dieta abarcando populações de diferentes estratos de renda (FERREIRA *et al.*, 2005). Em estudo realizado no Brasil, estimou-se que 46–79% da ingestão de arsênio inorgânico vem do arroz (CIMINELLI *et al.*, 2017).Além de arsênio, o arroz tem sido reconhecido como importante fonte de exposição a metais tóxicos, como chumbo, cádmio, e mercúrio, que são absorvidos da água e solo durante o cultivo, e por esta razão tem sido objeto de preocupação nos últimos anos (FU et al., 2015; JALLAD, 2015; KESHAVARZI et al., 2015;LIU et al., 2015)

A exposição a alguns elementos, mesmo em baixas doses, pode representar riscos importantes a saúde da população. Alguns metais são considerados interferentes endócrinos e os desfechos associados a exposições à baixas doses são doenças metabólicas, danos ao sistema reprodutivo, dentre outros (TCHOUNWOU et al., 2012; HAMPL et al., 2016). O câncer é um importante desfecho que tem sido associado à exposição à certos metais. (JAISHANKAR *et al.*, 2014). A *International Agency for Research on Cancer* (IARC) classifica o As, Cd, Al e Ni como carcinogênicos para humanos (grupo 1) e Pb como provavelmente carcinogênico para humanos (grupo 2) (IARC, 2020).

Estudo realizado por HUANG et al. (2013), demonstrou que, em alguns casos, a exposição a cádmio e chumbo por meio do consumo de arroz na China tem excedido os limites de ingestão diário considerados seguros para crianças e adultos.

Outro estudo identificou que a presença de chumbo, cadmio, metilmercúrio e arsênio total no arroz cultivado na China excederam os valores de referência estabelecidos pela FAO/WHO para chumbo, metilmercúrio e, principalmente, o arsênio (AL-SALEH; ABDULJABBAR, 2017).

Muitos dos elementos tóxicos encontrados em alimentos ocorrem naturalmente no ambiente, como cadmio, chumbo, alumínio e arsênio. Atividades antrópicas, como mineração e atividades industriais podem aumentar a concentração de tais elementos no ambiente, elevando a chance da absorção pelas plantas, que eventualmente podem ser consumidas pela população (U.S. FDA, 2016).

A exposição ao arsênio em arroz pela dieta não se mostra presente apenas pelo consumo deste cereal *in natura*. No mercado, há algumas opções de alimentos processados feitos de arroz ou farinha de arroz, como biscoitos, barras de cereais e principalmente cereais matinais infantis. Estes também podem conter elementos tóxicos oriundos do seu cultivo e/ou processamento, e merecem destaque pela faixa etária da população exposta e frequência de consumo em algumas culturas. A fase da vida em que ocorre a exposição pode se caracterizar como um importante fator de suscetibilidade, como a gestação, primeira infância e infância (Neto *et al.*, 2019; U.S. FDA, 2016). Em uma avaliação de riscos à saúde conduzida nos Estados Unidos da América (EUA), Shibata *et al.* (2016) avaliaram o risco da ingestão de arroz por crianças, incluindo arroz *in natura* e cereais matinais feitos de arroz. Os resultados indicaram riscos elevados e que demandavam medidas de intervenção.

Além de elementos potencialmente tóxicos presentes em cereais infantis, alguns pesquisadores têm alertado para o excesso de elementos essenciais neste tipo de alimento. A adição artificial de tais elementos essenciais, como zinco, manganês, e ferro, seguem uma estratégia de prevenção de desnutrição e algumas doenças na infância, o que pode ter resultados positivos significativos em alguns países em desenvolvimento, porém o excesso pode estar associado a danos à saúde, a depender do elemento e da dose (GARCIA-CASAL *et al.*, 2019).

Não apenas o arroz, mas a água pode ser uma importante fonte de exposição à arsênio. A ocorrência natural de arsênio em água subterrânea, como decorrência da presença de arsênio na composição das rochas, pode tornar este caminho de exposição muito relevante para a saúde pública. Esta é uma realidade em alguns países asiáticos, como certas localidades na Índia, Paquistão e Bangladesh (Upadhyay *et al.*, 2019; Lin *et al.*, 2015; Rahman, Asaduzzaman e Naidu, 2013). No Brasil, estudos apontam para concentrações mais elevadas de arsênio em água em localidades restritas, como resultado de atividades antropogênicas, principalmente a mineração, e em alguns casos a ocorrência natural em reservatórios subterrâneos (Costa *et al.*, 2015; Sakuma *et al.*, 2010; Figueiredo, Borba e Angélica, 2007; Borba, Figueiredo e Cavalcanti, 2004).

Agências internacionais têm dedicado especial atenção a exposição a baixas doses de iAs em alimentos e água. O limite máximo de arsênio inorgânico em arroz, em nível internacional, é determinado pelo Codex Alimentarius, que consiste em uma coleção de padrões, guias e códigos de conduta destinados a proteção da saúde, feitos pela Joint FAO/WHO *Codex Committee on Contaminants in Foods* e seus países membros. O limite vigente de iAs em arroz polido é 200 n g^{-1}, e em arroz integral é 350 n g^{-1} (Joint FAO/WHO, 2018). Cada país pode adotar uma regulamentação específica, e no Brasil este papel é executado pela Agência Nacional de Vigilância Sanitária (ANVISA), através da Resolução RDC n. 42/2013, que é destinada a estabelecer valores máximos de contaminantes inorgânicos em alimentos no

Mercosul, portanto tendo um caráter de regulação voltado para o comércio internacional, mas que se aplica também aos produtos de circulação nacional. O limite estabelecido pela ANVISA é de arsênio total, que para arroz polido e arroz integral é 300 n g^{-1} (BRASIL, 2013). Visando realizar uma padronização com os demais países do Mercosul e com as diretrizes internacionais, a ANVISA está em processo de adotar o limite para iAs em arroz, não mais arsênio total, alegando que a medida vigente dificulta as transações entre países, e que é mais restritiva que a diretriz internacional (ANVISA, 2020).

Nos Estados Unidos, a *Food and Drugs Administration* (FDA) realizou um estudo detalhado de revisão das evidências sobre efeitos associados à exposição ao arsênio. Foi avaliado o risco para a população do país estudado, e propostas medidas para mitigá-lo. Esta agência reconhece a avaliação de riscos como método importante para avaliar os riscos relacionados a alimentos contaminados e oferecer subsídios para estabelecer e avaliar estratégias para a gestão do risco, com o objetivo prevenir e mitigar os impactos na saúde da população (U.S. FDA, 2016).

Dado que o arroz é um alimento amplamente consumido no mundo, a recomendação internacional, em termos de prevenção à exposição ao arsênio, é adotar uma série de práticas para prevenir e reduzir a contaminação de arroz por arsênio. Tais medidas são voltadas principalmente a identificar e impedir as fontes de arsênio, bem como adotar práticas agrícolas reconhecidas por mitigar a concentração de iAs no grão (Joint FAO/WHO, 2011). Neste contexto, a avaliação de riscos é indicada pela *Food and Agriculture Organization* (FAO), ou Organização das Nações Unidas para a Alimentação e a Agricultura, como uma importante ferramenta para a gestão de riscos de alimentos com contaminantes químicos ou microbiológicos (FAO, 2015).

A avaliação quantitativa de riscos (AQR) é uma abordagem que permite estimar os riscos à saúde humana em decorrência da exposição à sustâncias químicas perigosas (NRC, 1983). Ela pode ser direcionada para uma população ou indivíduo, e tem como resultado um valor de risco, que é adimensional, e que pode ser interpretado como tolerável ou não de acordo com um valor de referência. (SWARTJES, 2015).

Esta ferramenta possui algumas vantagens em relação a outros métodos, como os estudos epidemiológicos ou o uso de biomarcadores, por exemplo. Pode-se elencar a possibilidade de se trabalhar com cenários hipotéticos de exposição; a realização de todas as etapas sem interferir na população estudada; baixo custo; a quantificação de valores baixos de risco; e trabalhar com casos de exposições passadas (NARDOCCI, 2010);

Em contrapartida, a AQR é uma medida indireta do risco; demanda modelos matemáticos e toxicológicos validados; e apresenta dificuldade de lidar com a multicausalidade para alguns desfechos, como o câncer (NARDOCCI, 2010).

As etapas da AQR e seus objetivos podem ser descritas como:

- Identificação do perigo: etapa destinada a realizar identificação de todos os agentes perigosos à saúde humana bem como o levantamento de suas propriedades físico-químicas e toxicológicas;
- Avaliação da exposição: é onde se realiza a identificação dos meios e caminhos de exposição ambiental e vias de exposição. São também realizadas as estimativas das doses recebidas pelos grupos expostos;
- Avaliação dose-resposta: tem como objetivo realizar a determinação da relação entre a magnitude da exposição, a dose, e a probabilidade de um efeito à saúde da população;
- Caracterização do risco: tem como objetivo realizar a descrição da natureza e da magnitude do risco à saúde humana (NRC, 1983).

A avaliação de riscos pode ser determinística ou probabilística, de modo que a segunda busca abarcar a variabilidade e a incerteza, que são inerentes a avaliação de riscos. A variabilidade refere-se à heterogeneidade encontrada em indivíduos de uma população e às diferenças na distribuição dos contaminantes do meio estudado (NIKOLAIDIS *et al.*, 2013). A variabilidade pode ser expressa por parâmetros estatísticos, como variância e desvio padrão. (U.S. EPA, 2014b).

A incerteza, diferente da variabilidade, pode ser tanto quantitativa como qualitativa, e refere-se à ausência de dados ou a incompreensão do contexto. Pode ser resultado de análises incompletas, erros de agregação, erros de julgamento, erros de amostragem, limitação de modelos, entre outros. A aquisição de mais dados ou dados de maior qualidade são o caminho para a redução da incerteza (U.S. EPA, 2014b).

Na avaliação de riscos, a adoção de uma abordagem probabilística permite a caracterização da variabilidade e incerteza. Esta é uma abordagem considerada mais complexa em relação à abordagem determinística, mas que também apresenta vantagens (MORISSET *et al.*, 2013).

Na avaliação de determinística usa-se valores médios ou máximos como valores de entrada, e tem-se com resultado um valor pontual de risco. Apesar de não considerar a variabilidade e incertezas, tem como vantagens a baixa complexidade e menor custo (U.S. EPA, 2014b).

A avaliação probabilística usa como valores de entrada uma distribuição de dados, onde são sorteados múltiplos pontos para cada parâmetro. Este processo é repetido uma série de vezes, de modo que cada sorteio gera um resultado que compõe uma distribuição de potenciais valores de risco (U.S. EPA, 2014b).

O repetido sorteio dos valores de uma ou mais distribuições de entrada é responsável por caracterizar a variabilidade e incerteza. Por exemplo, pode-se sortear valores para peso corporal, frequência de exposição e/ou concentração de contaminante no meio. Tais variáveis são independentes e representam a variabilidade dentro da população ou meio estudado. Para cada iteração (repetição) configura-se uma combinação de valores de entrada, e gera como resultado uma distribuição da possível estimação de risco (U.S. EPA, 2014b).

Assim é possível caracterizar a heterogeneidade da população exposta (devido a questões fisiológicas), e da distribuição da contaminação no meio de estudo (NIKOLAIDIS, et al., 2013; U.S. EPA, 2001).

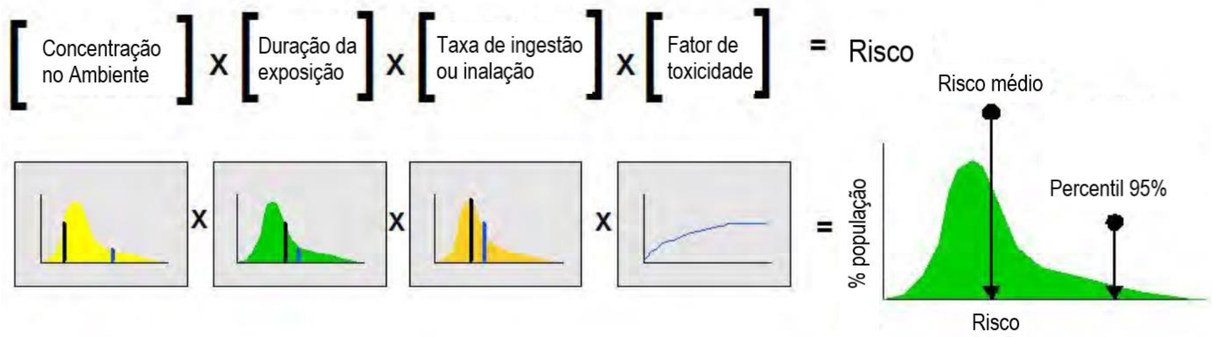
Destaca-se ainda que avaliação probabilística permite gerar estimativas de exposição de acordo com os percentis, possibilitando trabalhar com as estimativas mais conservadoras (por exemplo de 95 ou 99%), os quais representam os piores casos de exposição e os riscos para os grupos mais expostos (U.S. EPA, 2014b).

A avaliação probabilística é mais sofisticada, e tem custos mais elevados. Demanda um conjunto maior de dados do monitoramento do compartimento ambiental estudado e dados de qualidade, equipe qualificada, softwares específicos, além de maior tempo para sua realização (U.S. EPA, 1997).

Assim, esta é mais indicada, por exemplo, quando os resultados da abordagem determinística indicam riscos à saúde não toleráveis; quando o custo da intervenção e gestão do risco é muito elevado; e em cenários de elevadas incertezas (U.S. EPA, 1997). Quase toda avaliação de riscos tem com etapa inicial a realização de uma avaliação determinística (HEALTH CANADA, 2010).

Para realizar a avaliação probabilística é necessária a adoção de um método, sendo o que mais utilizado é o método de Monte Carlo (Morisset, Ramirez-Martinez, Wesolek, & Roudot, 2013). Este método usa de softwares computacionais para realização de amostragens aleatórias da distribuição da probabilidade para cada variável. Tal processo é repetido diversas vezes (usualmente dez mil), e cada iteração produz uma única estimativa de risco. O resultado das iterações define a probabilidade da distribuição do risco, que pode ser representado em um histograma, facilitando a sua visualização (Health Canada, 2010). Um esquema da simulação Monte Carlo é apresentado na figura 1.

Figura 1 - Esquema ilustrativo do Método de Monte Carlo



Adaptado de: (U.S. EPA, 2014)

A aplicabilidade do método de Monte Carlo é bastante genérica, o que é sua principal vantagem. Ele aceita qualquer forma de distribuição de entrada, não oferece restrições à natureza da relação entre os dados de entrada e saída, e seu manuseio no computador é relativamente fácil. Em contrapartida tem a necessidade de uma distribuição de dados confiáveis; é difícil avaliar a sensibilidade dos resultados em relação aos dados de entrada; e caso se altere algum valor, é necessário realizar todas as estimativas novamente (U.S. EPA, 1992).

A avaliação de riscos tem sido indicada pela FAO e FDA como uma importante ferramenta para avaliar riscos na área de alimentos, e considerada relevante para oferecer subsídios no estabelecimento de estratégias de gestão do risco, sendo ressaltada a vantagem da avaliação probabilística para esta área, que por natureza possui variabilidade e pode possuir incertezas (U.S. FDA, 2016; FAO, 2015).

A Organização Mundial da Saúde (OMS) e a FAO reconhecem que a contaminação de alimentos por elementos químicos potencialmente tóxicos à saúde humana, especialmente o arroz, é um problema de importância para a saúde pública e que mais estudos são necessários para que se possam dar diretrizes adequadas para consumidores e produtores de arroz (JOINT FAO/WHO, 2011a).

O acesso a alimentos de qualidade, bem como a promoção da saúde, faz parte do conceito de Segurança Alimentar e Nutricional, que é estabelecido como um direito pela Lei Orgânica de Segurança Alimentar, nº 11.346 de 15 de setembro de 2006. Portanto não só o alimento é um direito, mas também alimentos que não ofereçam riscos significativos à saúde das pessoas (BRASIL, 2006).

Além disto, alcançar a segurança alimentar está dentre os 17 Objetivos do Desenvolvimento Sustentável propostos pela Organização das Nações Unidas (ONU) de 2015, expresso no objetivo 2 “Acabar com a fome, alcançar a segurança alimentar e melhoria da nutrição e promover a agricultura sustentável” (ONUBR, 2017).

Apesar da importância que o arroz tem para a alimentação da população brasileira, estudos sobre os riscos associados a exposição a arsênio e outros elementos tóxicos, em especial associados a efeitos de baixas doses, são escassos. A exposição crônica, em especial de grupos suscetíveis, como gestantes e crianças, deve ser priorizada (NAUJOKAS *et al.*, 2013). Entender os riscos aos quais a população está exposta é primeiro passo para a correta gestão dos riscos em prol da saúde pública.

3. OBJETIVOS

1.1. OBJETIVO PRINCIPAL

Avaliar o risco de efeitos carcinogênico e não carcinogênico para a população brasileira devido ao consumo de arroz e cereais infantis feitos de arroz referente à presença elementos tóxicos, principalmente o arsênio, e elementos essenciais.

1.2. OBJETIVOS ESPECÍFICOS

- Investigar se há diferença no risco referente ao consumo de arroz branco e integral;
- Identificar possíveis medidas de mitigação do risco para consumo de arroz no Brasil;
- Identificar a contribuição do consumo de água para os riscos associados à exposição ao arsênio inorgânico;
- Verificar se cereais infantis feitos de arroz oferecem maior risco que cereais infantis feitos de outros tipos de ingredientes;
- Investigar se outros elementos (tóxicos e essenciais) presentes em arroz e cereais infantis podem oferecer riscos à saúde.

4. MATERIAIS E MÉTODO

A estimativa do risco será realizada seguindo as recomendações da *United States Environmental Protection Agency* (U.S.EPA), iniciando-se pelo cálculo da dose média diária da população exposta, que leva em consideração a concentração de contaminantes no alimento, a quantidade e a frequência de ingestão do alimento, o peso corpóreo e o tempo de exposição. A dose é utilizada para o cálculo do incremento de risco no tempo de vida, e do quociente de perigo para a avaliação do riso não carcinogênico, conforme detalhado nas seções seguintes (USEPA, 1989).

4.1. DOSE, RISCO E QUOCIENTE DE PERIGO

A dose média diária, do inglês *average daily dose* (ADD), foi estimada separadamente para cada caminho de exposição (ingestão de arroz branco, arroz integral, cereais infantis e água), de acordo com a equação:

$$ADD_j = \frac{[C \times IRj \times EDj \times EFj]}{[BWj \times AT]} \qquad (1)$$

Onde ADDj é a dose diária média (mg/kg-dia) para o grupo etário j; C é a concentração do elemento químico no alimento ou água (mg/g ou mg/ml); IR é a taxa de ingestão do alimento ou água (g/dia ou ml/dia) para o grupo etário j; EDj e EFj são, respectivamente, a duração da exposição (anos) e a frequência da exposição (dias/ano) para o grupo etário j; BWj é o peso corpóreo para o grupo etário j; e AT é o tempo médio da exposição, calculado por EDj × 365 dias.

O risco carcinogênico foi calculado para cada grupo etário, de modo a representar as diferenciações do risco no tempo de vida. A soma ponderada do risco para cada grupo etário resultou no incremento de risco de câncer no tempo de vida (ILCR) (U.S. EPA, 2005):

$$ILCR = \sum_{j=1,n} (ADDj \times SF) \times \frac{ED_j}{LT}) \qquad (2)$$

Onde o SF é o *slope factor*, ou fator de carcinogenicidade, do agente químico; LT é o tempo de vida (70 anos) e n é o número de grupos etários.

O risco não carcinogênico foi calculado pelo Quociente de Perigo (HQ), ou em inglês *Hazard Quotient* como é também referido, para cada caminho de exposição. Para tanto, primeiramente foram estimadas frações de HQ para cada grupo etário pela divisão de ADDj pela RfD, que é a dose de referência para o agente químico. A soma das frações de HQ de cada grupo etário j (considerando n grupos etários) ponderada pela duração da exposição j e tempo de vida resultou no HQ:

$$HQ = \sum_{j=1,n} \left(\frac{ADD_j}{RfD}\right) \times \frac{ED_j}{LT} \qquad (3)$$

A vantagem de se calcular o HQ fracionado é identificar as diferentes contribuições ao HQ no tempo de vida, além de se reduzir a incerteza.

Para substâncias que possuem reconhecidamente os mesmos efeitos não-carcinogênicos à saúde, os HQs calculados foram somados a fim de obter-se o *Hazard Index* (HI) (U.S. EPA, 1989).

As estimativas do ILCR e HQ para ingestão de arroz (branco e integral) e água foram realizadas seguindo uma abordagem probabilística, através de simulação Monte Carlo, utilizando como parâmetros de entrada distribuições da concentração de arsênio inorgânicos e outros elementos presente em arroz, e arsênio inorgânico em água potável. Para esta avaliação probabilística foram feitas 10.000 iterações e com intervalo de confiança de 95% por meio do software YASAIw, do State of Washington Department of Ecology (PELLETIER; BOX, 2009). Os demais parâmetros, como peso corpóreo, não foram inseridos na forma de distribuição, por não apresentaram um bom ajuste a nenhuma distribuição. A avaliação de riscos referente aos cereais infantis foi realizada seguindo uma abordagem determinística, ou seja, utilizando valores médios dado a limitada quantidade de amostras de cereais infantis disponível.

4.2. CONCENTRAÇÃO DE ARSÊNIO INORGÂNICO, ELEMENTOS TÓXICOS E ELEMENTOS ESSENCIAIS

Para este trabalho foram utilizados dados secundários da concentração dos elementos químicos em arroz, cereais infantis e água.

A concentração de elementos essenciais e não essenciais presentes em arroz foram obtidos de uma pesquisa conduzida no Brasil que coletou a analisou 154 amostras de arroz do Brasil (64 amostras de arroz branco, e 90 amostras de arroz integral). Os elementos tóxicos e essenciais são 21: As (apenas iAs), Al, B, Ba, Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Ni, Na, P, Pb, Se, Sr, e Zn (BATISTA, 2015).

A concentração de elementos tóxicos e essenciais em cereais infantis provém de um estudo conduzido no Brasil, onde os autores coletaram 18 amostras de cereais infantis, sendo que nove tem o arroz como componente básico, cinco são cereais multi-grão que contém arroz, e quatro são cereais que não contém arroz na composição. Esta pesquisa conseguiu dados de concentração de 22 elementos: Ag, Al, As, B, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Ni, Na, Pb, Se, Sr, e Zn (PEDRON *et al.*, 2016).

Foram incluídos na avaliação de riscos apenas elementos com um *slope factor* (SF) ou dose de referência (RfD) descritos na literatura científica.

Os dados de concentração de arsênio em água são provenientes do Sistema de Informação de Vigilância da Qualidade da Água para o Consumo Humano (SISAGUA), que armazena dados da qualidade da água em nível nacional. Os dados correspondem a concentração de arsênio total em 3.466 amostras coletadas entre 2014 e 2018 disponível em 15 estados do Brasil (BRANDT; AQUINO; BASTOS, 2019)

4.3. CONSUMO DE ALIMENTOS E ÁGUA, FREQUENCIA DE EXPOSIÇÃO E PESO CORPÓREO

O consumo de arroz foi obtido de diferentes fontes a fim de compor o consumo no tempo de vida. De 4 meses a 1 ano e de 5 a 10 anos de idade o consumo de arroz foi estimado com base no Manual de Orientação para Centros de Educação Infantil (SÃO PAULO, 2011ª; SÃO PAULO, 2011b). De 1 a 5 anos de idade o consumo de arroz foi obtido de um estudo realizado em duas creches em São Paulo (LEROUX *et al.*, 2018). Para grupos etários entre 10 e 70 anos, os valores são da Pesquisa de Orçamentos familiares realizada pelo Instituto Brasileiro de Geografia e Estatística (IBGE) com dados de 2008 e 2009 (IBGE, 2020).

A ingestão de cereais infantis foi estimada de acordo com a taxa descrita pelo *Child-specific Exposure Factors Handbook* (U.S. EPA, 2009) determinada em g de cereais infantis por kg do peso corpóreo. Assim a taxa para cada idade foi multiplicada pelo peso corpóreo da população brasileira (IBGE, 2010)

A ingestão de água foi calculada pela ingestão de água do *Exposure Factors Handbook* (U.S. EPA, 2019) em relação ao peso corpóreo por dia (ml/kg-dia) da população brasileira (IBGE, 2010). O peso corpóreo foi calculado pela média ponderada entre homens e mulheres em relação à população total entrevistada (IBGE, 2010).

A frequência de exposição para arroz foi considerada 6 dias/semana (312,85 dias/ano); para água foi 7 dias/semana (365 dias/anos), bem como para cereais infantis (SHIBATA *et al.*, 2016).

4.4. ANÁLISE ESTATÍSTICA DOS DADOS

A análise estatística foi feita pelo software R, versão 3.5.0, e R studio, versão 1.1.453 (*The R Foundation for Statistical Computing, Vienna, Austria*). Para ajustar os dados (concentração de arsênio inorgânico e outros elementos presentes em arroz, e arsênio total em água) à uma distribuição, o pacote fitdistplus foi adotado. Foram testadas as distribuições normal, lognormal e exponencial, e foi escolhida a que apresentou menor valor de Akaike information criterion (AIC).

Apesar da disponibilidade de dados referentes ao consumo de alimentos e água, e peso corpóreo para cada grupo etário, em conjunto eles não apresentaram um bom ajuste a nenhuma distribuição. Portanto, optou-se em calcular a dose, risco e HQ fracionário para cada grupo etário, de modo que a soma ponderada dos mesmos corresponderia ao ILCR ou HQ no tempo de vida. Esta abordagem apresentou a vantagem de permitir a identificação dos grupos etários mais vulneráveis, o que pode ser valioso na gestão do risco.

5. RESULTADOS E DISCUSSÃO

Manuscrito I: Cancer risk associated with exposure to inorganic arsenic in rice and drinking water in Brazil: A human health risk assessment.

Artigo submetido para revista científica.

Manuscrito II: Risk assessment from exposure to essential and toxic elements in infant cereal in Brazil.

Artigo pronto para revisão gramatical da língua inglesa.

Manuscrito III: Probabilistic risk assessment from exposure to essential and non-essential elements in rice from Brazil.

Artigo submetido para revista científica.

5.1. MANUSCRITO I

Cancer risk associated with exposure to inorganic arsenic in rice and drinking water in Brazil: A human health risk assessment.

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ABSTRACT

In certain populations, rice is the main source of exposure to inorganic arsenic (iAs), which is classified as a Group 1 carcinogen and is also associated with non-cancer effects. Although rice is a staple food in Brazil, there have been few studies about the health risks for the Brazilian population. The objective of this study was to assess the risks of exposure to iAs from polished (white) rice, husked (brown) rice, and drinking water in Brazil, in terms of the carcinogenic and non-carcinogenic effects, and to propose measures to mitigate those risks. The incremental lifetime cancer risk (ILCR) and hazard quotient (HQ) were calculated. A probabilistic analysis was performed with Monte Carlo simulation. The mean ILCR was 1.4×10^{-04} for white rice and 5.7×10^{-06} for brown rice. The HQ for white and brown rice was under 1. The ILCR for water consumption was 6.5×10^{-05}, corresponding to 32% of the total risk for white rice and water consumption and 90% of that for brown rice and water consumption. The HQ for water consumption was below 1 in all age groups. Various mitigation measures discussed in this report are estimated to reduce the risk from rice consumption by 6–68%. The ILCR for white and brown rice was high, despite the fact that the iAs concentration in rice is below the maximum contaminant level. The risk for brown rice consumption was lower because the iAs concentrations were low in the brown rice samples evaluated. The cancer risk for water consumption is above the tolerable value of 1×10^{-5} recommended by the World Health Organization. With the support of public policies, measures to reduce these risks for the Brazilian population, focusing on the risk from white and brown rice, would have a positive impact on public health.

Keywords:

Probabilistic risk assessment

Hazard quotient

Monte Carlo

Toxic elements

Food safety

Food contaminants

1. Introduction

Although arsenic exists in various chemical forms, it is mainly categorized, from a public health perspective, as organic or inorganic. These different forms occur naturally in the environment, and anthropogenic activities can substantially increase their concentration and bioavailability in soil and water, allowing them to be absorbed by plants in agricultural fields. Inorganic arsenic (iAs) is classified as a Group 1 carcinogen and is present in trace amounts in rocks, soil, air, food, and water (IARC, 2012; WHO, 2012). Food and water are the most important sources of exposure to iAs, and rice (*Oryza sativa*) is the main source of exposure in some populations (EFSA, 2014; U.S. FDA, 2016). Rice is usually cultivated in flooded fields, where the anaerobic conditions increase iAs availability in soils. Arsenate is reduced to the more mobile arsenite, leading to a higher concentration of both forms close to the plant roots. Arsenate and arsenite are analogues of the plant micronutrients phosphate and silicic acid, respectively, therefore being easily taken up and stored by the plant. Fertilizers, pesticides, and the water used to irrigate the crops can also be sources of iAs (Joint FAO/WHO, 2017; Zhao et al., 2010).

Rice is a staple food for more than half of the world population, accounting for approximately 30% of the energy intake and 20% of the protein intake; it can therefore be a significant source of iAs and other metals (Fu et al., 2015; Gross and Zhao, 2014; Ma et al., 2017). The European Food Safety Authority recognized rice as the main source of iAs for the European population (EFSA, 2014). In Asia, rice is also a staple food and tends to be the major source of iAs from food (Joint FAO/WHO, 2011). In a study conducted in China (Al-Saleh and Abduljabbar, 2017), the concentrations of iAs and other metals in rice were found to be above the maximum contaminant levels (MCLs) established by the United Nations Food and Agriculture Organization and the World Health Organization (FAO/WHO).

In Brazil, rice is one of the main components of daily meals and is consumed by the entire population, regardless of socioeconomic status. The average daily consumption of rice by adults is estimated to be 140.9 g (IBGE, 2020), which is comparable to that reported for some locations in China (Li et al., 2011). Rice consumption accounts for 46–79% of the iAs ingested by the Brazilian population (Ciminelli et al., 2017).

Epidemiological studies have shown that exposure to iAs is associated with cancer of the lung, bladder, kidney, skin, liver, and prostate (IARC, 2012). The non-cancer effects from long-term oral exposure to iAs include dermal, cardiovascular, respiratory, and neurodevelopmental changes, and acute high-dose oral exposure has been associated with nausea, vomiting, diarrhea, and encephalopathy (ATSDR, 2007). The susceptible life stages are pregnancy, infancy, and early childhood (U.S. FDA, 2016). The Joint FAO/WHO Expert Committee on Food Additives recognizes iAs in rice as a public health concern (Joint FAO/WHO, 2011), and quantitative risk assessment has been considered an important tool for risk management and to support decision-making in public health (FAO, 2015).

Only a few studies have evaluated exposure to iAs in rice in Brazil (Batista et al., 2011; Ciminelli et al., 2017). The available studies evaluating exposure to iAs in drinking water have focused mainly on areas contaminated by mining activities, such as some localities in the state of Minas Gerais and in the Amazon region, although not on Brazil as a whole (Costa et al., 2015; Figueiredo et al., 2007; Sakuma et al., 2010). In the present study, we focused on a probabilistic analysis of the risk of exposure to iAs in polished (white) and husked (brown) rice from Brazil, as well as of that of exposure to drinking water in Brazil. Hypothetical scenarios of risk reduction were also assessed. Cancer and non-cancer risks were estimated using the slope factor and the U.S. Environmental Protection Agency (EPA) reference dose for iAs (U.S. EPA, 1995).

2. Method

2.1. Average daily dose, cancer risk, and hazard quotient

The average daily dose by exposure pathway was estimated according to the following equation (U.S. EPA, 1989):

$$ADD_j = \frac{[C \times IRj \times EDj \times EFj]}{[BWj \times AT]} \qquad (1)$$

where *ADDj* is the average daily dose in mg/kg-day for the age group *j*; *C* is the concentration of iAs in raw rice (mg iAs/g rice) or drinking water (mg iAs/ml water); *IRj* is the ingestion rate of rice (g rice/day) or drinking water (ml water/day) for the age group *j*; *EDj* and *EFj* are the exposure duration (years) and exposure frequency (days/year) for the age group *j*, respectively; *BWj* is the body weight for the age group *j*; and *AT* is the average time, which is the *EDj* × 365 days.

As the exposure varies with age, the incremental lifetime cancer risk (ILCR) was estimated by summing the cancer risk in each age group (U.S. EPA, 2005), as follows:

$$ILCR = \sum_{j=1,n} (ADDj \times SF) \times \frac{ED_j}{LT}) \qquad (2)$$

where *SF* is the slope factor for oral iAs, which is 1.5 $(mg/kg\text{-}day)^{-1}$ (U.S. EPA, 1995), and LT is the lifetime, which is 70 years, and n is the number of age intervals.

The risk of non-cancer effects (cardiovascular and dermal outcomes) was estimated by the hazard quotient (HQ) summing the fractional HQ of each age group, which is the ADDj divided by the RfD weighted by exposure duration j:

$$HQ = \sum_{j=1,n} \left(\frac{ADD_j}{RfD}\right) \times \frac{ED_j}{LT} \qquad (3)$$

where *RfD* is the reference dose for oral exposure to iAs, which is 0.003 mg/kg per day (U.S. EPA, 1995), and n is the number of age intervals.

The ILCR and HQ calculations were implemented in a probabilistic framework, with a Monte Carlo simulation of 10,0000 iterations, with a confidence interval of 95%. The simulations were performed using distributions for the concentration of arsenic in rice and water. The probabilistic assessment was carried out in the open-source software YASAIw, from the State of Washington Department of Ecology (Pelletier and Box, 2009).

2.2. Concentration of iAs in Brazilian rice

The data related to the concentrations of iAs in white and brown rice were obtained from a study conducted by Batista et al. (2015), one of the few studies about iAs in rice from Brazil, which we had access. In that study, samples of raw rice were collected from different areas in Brazil, mainly the southern region, which is the largest rice-producing region in the country. There were 64 samples of white rice (all obtained from markets), and 90 samples of brown rice (69 from farms and 21 from markets). The authors evaluated total arsenic and iAs using high-performance liquid chromatography with inductively coupled plasma mass spectrometry. The authors evaluated the total concentration of As by microwave digestion of the rice samples, as described by Paniz et al. (2018). The samples were ground, sieved (<250 µm), and weighed (200 mg) in triplicate, and then placed in 100-mL polytetrafluoroethylene vessels, where 4 mL of sub-distilled HNO_3 (20 vol%) and 1 mL of H_2O_2 (30 vol%) were added. The tubes were then placed in a microwave system (up to 35 bar). After cooling, ultrapure water was added to make up 50 mL, and then the samples were analyzed by ICP-MS. The speciation analysis was performed as described by Batista et al. (2011). The samples, in two replicates, containing about 200-mg of ground and sieved (<250 µm) rice, were weighed into 50-mL conical tubes, treated with 10 mL of HNO_3 (2 vol%), and then stirred (100 rpm) for 24 h. In sequence, the tubes were heated (95 °C) in a water bath for 2.5 h. Finally, after cooling, the samples were filtered and analyzed by HPLC-ICP-MS.

2.3. Rice consumption

Because there are no available data regarding daily consumption of brown rice in Brazil, the same rates were considered for white and brown rice. The rice consumption for each age group, which includes only rice grain consumption (not rice derived products, such as rice flour present in certain kinds of food) was obtained from different sources, as also presented in table S.1, in supplementary material:

- 4 months to 1 year and 5 to 10 years—the estimated rice consumption was based on the quantity recommended by the São Paulo Municipal Department of Education for consumption in schools and daycare centers (São Paulo, 2011a; São Paulo, 2011b). Because we noticed that the recommended consumption was overestimated in comparison with the actual consumption for children 1 to 5 years of age (see below), we estimated that the actual rice consumption for children 4 months to 1 year and 5 to 10 years of age was 39.8% less than that. In the school diet, rice is served cooked (as a side dish, in soups, or as a dessert) and the quantities were registered in grams of raw rice. Students from 6 to 10 years of age have a part-time school period, having only one meal at school (lunch or dinner), and daily rice consumption for that age group was therefore estimated on the basis of the recommended quantity.
- 1 to 5 years—data were obtained from a study involving 64 children at two daycare centers in the city of São Paulo (Leroux et al., 2018), in which 24-h duplicate diet samples were analyzed by inductively coupled plasma mass spectrometry and the portions were recorded, including the food consumed at the daycare center and that consumed at home. The consumption of rice and soup containing rice was evaluated. Household measures (*e.g.*, tablespoons) were converted to grams in accordance with nutrition guidelines (Bompem et al., 2012; Tomita and Cardoso, 2000).
- 10 to 70 years—data were obtained from a study conducted by the Brazilian Institute of Geography and Statistics (IBGE, 2020), in which the consumption of cooked rice in the last 48 h was determined on the basis of self-reports by interviewees in all Brazilian states, from 10 to 70 years.

2.4. Concentration of arsenic in drinking water

The data related to total As in drinking water were obtained from the study conducted by Brandt et al. (2019). The authors evaluated 3,466 water samples collected between 2014 and 2018 via the Drinking Water Quality Surveillance database of the Brazilian National Ministry of Health (BNMH). This database have only data about total As available, not iAs. The samples were collected in 15 states from the five regions of Brazil (Bahia, Ceará, Espírito Santo, Goiás, Minas Gerais, Mato Grosso do Sul, Mato Grosso, Pará, Paraná, Rio de Janeiro, Rio Grande do Sul, Santa Catarina, Sergipe, Sao Paulo and Tocantins). Data under the limit of detection (LOD) or limit of quantification (LOQ) was replaced by LOD/2 or LOQ/2, respectively. Outliers (2) and samples with concentration of iAs of 0 and no LOD described were excluded (33).

2.5. Drinking water ingestion rate

The consumption of drinking water was estimated by calculating the drinking water ingestion rates (ml/kg per day), as recommended in the EPA Exposure Factors Handbook (U.S. EPA, 2019), multiplied by the reference body weight values for the Brazilian population (IBGE, 2010).

2.6. Body weight

Body weight was also obtained from the study conducted by the Brazilian Institute of Geography and Statistics (IBGE, 2010). Body weight was calculated by the weighted average of the male and female population, in relation to the total of interviewed individuals.

2.7. Exposure frequency

Because rice is a staple food in Brazil, the exposure frequency (EF) for rice was considered to be 6 days/week (312.85 days/year). For drinking water, the exposure frequency (EF) was considered to be 7 days/week (365 days/year).

2.8. Statistical analysis

The statistical analysis was conducted with R software, version 3.5.0, and R studio, version 1.1.453 (The R Foundation for Statistical Computing, Vienna, Austria). We used the fitdistrplus package in order to fit the distribution of the iAs concentration data sets. The 64 white rice and 90 brown rice iAs concentrations from Batista et al. (2015) and 3,431 iAs water concentrations from Brandt et al. (2019) were fit using the normal, lognormal and exponential distribution assumptions available in the fitdistrplus package. The distribution with the lowest Akaike information criterion value was selected. Pearson’s correlation coefficient was calculated to identify a correlation between iAs and cadmium in rice as evidence of water management during rice cultivation.

Table S.1 summarizes the exposure parameters, body weight and rice dietary and drinking water consumption rates for various age groups, obtained or estimated from the sources described above and adopted for the risk assessment.

The data for rice consumption and body weight did not have a good fit in any distribution, so to minimize the uncertainty avoiding using mean values for the lifetime, the risk was assessed for age groups. The advantage of this approach is to obtain risk results for each age group, being possible to identify which is more vulnerable.

2.9. Hypothetical scenarios of risk reduction

Adopting the same dose–response model for each of six different scenarios, we assessed hypothetical interventions intended to reduce the risk. The objective was to simulate the impact of different mitigation strategies, some of which were proposed by the U.S. Food and Drug Administration (FDA)—such as lowering the MCL or interrupting the exposure of infants and children)—whereas others were based on our results.

3. Results and discussion

Figure 1 shows a box plot of iAs concentrations in white and brown rice. Table S.2 (in the supplementary material) shows the descriptive statistics. The normal distribution had the best fit for the white rice data set (mean, 100.2 ± 44.6), whereas the log-normal distribution had the best fit for the brown rice data (μ = 4.1; δ = 0.9).

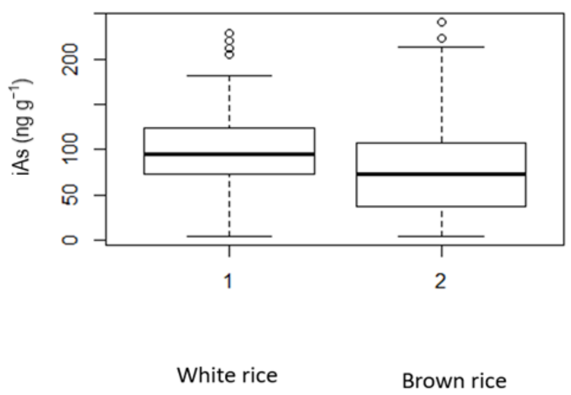

Fig. 1. Box plot of inorganic arsenic (iAs) concentrations in polished (white) and husked (brown) rice.

3.1. Cancer risk associated with exposure to iAs in rice

Table 1 presents the results of cancer risk by age and ILCR, and table S.3 (in the supplementary material) presents the ADD by age. The mean and 95th percentile incremental lifetime cancer risk (ILCR) were 1.4×10^{-04} and 2.3×10^{-04} for white rice and 5.4×10^{-06} and 7.7×10^{-06} for brown rice. The incremental risk is higher for infants and children 1 ≤ 6 years of age. Rice consumption starts at an early age in Brazil. According to food consumption guidelines for daycare centers in the city of São Paulo, the consumption of rice and other kinds of solid food starts at 4 months of age (São Paulo, 2011a). Because the standard maternity leave in Brazil is 120 days (Brasil, 2016), exclusive breastfeeding until 6 months of age, as recommended by the WHO (WHO, 2017a), is a challenge. Measures to increase maternity leave in the country have recently been proposed. Since 2008, civil servants have 180 days of maternity leave and there are tax incentives for companies that grant 180 days of maternity leave to their employees (Brasil, 2008). However, the proportion of the workforce protected by labor laws that guarantee maternity leave has decreased (Brasil, 2009).

Table 1 – Estimated incremental cancer risks and incremental lifetime cancer risk (means and 95th percentiles) associated with exposure to inorganic arsenic in polished (white) and husked (brown) rice.

Age (years) and ILCR	White rice cancer risk		Brown rice cancer risk	
	Mean	95th percentile	Mean	95th percentile
< 1	1.62×10^{-06}	2.78×10^{-06}	6.47×10^{-08}	9.15×10^{-08}
1	9.20×10^{-06}	1.57×10^{-05}	3.66×10^{-07}	5.18×10^{-07}
2	7.40×10^{-06}	1.26×10^{-05}	2.95×10^{-07}	4.17×10^{-07}
3	7.23×10^{-06}	1.24×10^{-05}	2.88×10^{-07}	4.08×10^{-07}
4	7.03×10^{-06}	1.20×10^{-05}	2.80×10^{-07}	3.96×10^{-07}
5	5.52×10^{-06}	9.44×10^{-06}	2.20×10^{-07}	3.11×10^{-07}
6	5.09×10^{-06}	8.71×10^{-06}	2.03×10^{-07}	2.87×10^{-07}
7	4.52×10^{-06}	7.73×10^{-06}	1.80×10^{-07}	2.55×10^{-07}
8	4.08×10^{-06}	6.97×10^{-06}	1.62×10^{-07}	2.30×10^{-07}
9	3.57×10^{-06}	6.10×10^{-06}	1.42×10^{-07}	2.01×10^{-07}
10	2.66×10^{-06}	4.54×10^{-06}	1.06×10^{-07}	1.50×10^{-07}
11	2.36×10^{-06}	4.03×10^{-06}	9.39×10^{-08}	1.33×10^{-07}
12	2.09×10^{-06}	3.57×10^{-06}	8.31×10^{-08}	1.18×10^{-07}
13	1.89×10^{-06}	3.22×10^{-06}	7.51×10^{-08}	1.06×10^{-07}
14	1.75×10^{-06}	3.00×10^{-06}	6.99×10^{-08}	9.89×10^{-08}
15	1.64×10^{-06}	2.80×10^{-06}	6.52×10^{-08}	9.23×10^{-08}
16	1.58×10^{-06}	2.70×10^{-06}	6.30×10^{-08}	8.91×10^{-08}
17	1.53×10^{-06}	2.61×10^{-06}	6.09×10^{-08}	8.61×10^{-08}
18	1.49×10^{-06}	2.55×10^{-06}	5.93×10^{-08}	8.38×10^{-08}
19	1.51×10^{-06}	2.57×10^{-06}	5.99×10^{-08}	8.48×10^{-08}
20 to <25	7.22×10^{-06}	1.23×10^{-05}	2.88×10^{-07}	4.07×10^{-07}
25 to <30	6.90×10^{-06}	1.18×10^{-05}	2.75×10^{-07}	3.89×10^{-07}
30 to <35	6.77×10^{-06}	1.16×10^{-05}	2.70×10^{-07}	3.82×10^{-07}
35 to <45	1.34×10^{-05}	2.28×10^{-05}	5.32×10^{-07}	7.52×10^{-07}
45 to <55	1.32×10^{-05}	2.26×10^{-05}	5.27×10^{-07}	7.46×10^{-07}
55 to <65	1.22×10^{-05}	2.10×10^{-05}	4.88×10^{-07}	6.90×10^{-07}
65 to <70	2.89×10^{-06}	4.94×10^{-06}	1.15×10^{-07}	1.63×10^{-07}
ILCR	1.36×10^{-04}	2.33×10^{-04}	5.43×10^{-06}	7.68×10^{-06}

ILCR: incremental lifetime cancer risk.

The ILCR for exposure to iAs in white rice obtained in our study is lower than that reported for other countries where rice is also a staple food. In Saudi Arabia, Al-Saleh and Abduljabbar (2017) found a mean ILCR of 5.8×10^{-2} (minimum of 1.2×10^{-2} and maximum of 2.6×10^{-1}). The authors used the concentrations of total arsenic but estimated that iAs represented 80–90% of the total. Another probabilistic risk assessment, conducted in China by Li et al. (2011), found an average ILCR of 1.77×10^{-3}, higher than that found in the present study. Those authors evaluated the consumption of white rice and other foods, such as rice flour, coarse cereals, vegetables, fruit, meat, milk, eggs, and aquatic products. They found that the most relevant variable was the rate of ingestion of aquatic products, followed by the iAs concentration in rice. The ILCR varied among the different areas of the country, and the authors concluded that the risk was mainly explained by the kind of food consumed and the ingestion rate.

In Taiwan, Chen et al. (2016) found the mean ILCR for exposure to iAs in white and brown rice to be 1.04×10^{-4} for males and 7.87×10^{-5} for females. The mean ILCR for exposure to iAs in white rice was reported to be 2.06×10^{-4} in Punjab, India (Sharma et al., 2020). These results are similar to the result found in our study.

A major risk assessment conducted in the United States by the FDA found a median ILCR of 3.4×10^{-5} for white rice (with a 5% and 95% confidence limits of 0 and 6.9×10^{-5}, respectively) and 5.4×10^{-6} for brown rice (0 and 1.1×10^{-5} are the confidence limits of 5% and 95%, respectively) (U.S. FDA, 2016), both of which are lower than the values found in our study. That could be attributed to the fact that rice consumption is higher in Brazil. The authors of that study also calculated the risk associated with a higher, but still lower than that reported for Brazil, per-serving (per eating occasion) dose level. On that basis, the median risk would be 1.36×10^{-4} for white rice (0 and 2.78×10^{-4} are the 5% and 95% confidence limits, respectively) and 1.64×10^{-4} for brown rice (0 and 3.38×10^{-4} are the 5% and 95% confidence limits, respectively.

The high ILCR values found in the present study are mainly associated with the elevated rice consumption in Brazil, which is on average for all age groups 156.6 g/day, compared with 17.1 g/day (including rice flour) in the United States (U.S. FDA, 2016). According to Meharg (2007), rice consumption is also very low (10.0 g/day) in the United Kingdom. However, rice consumption is much higher in most Asian countries, such as China, where the daily rice consumption can be as high as 218.64 g (Song et al., 2017), as well as Bangladesh, Laos, and Myanmar, where it ranges from 400.0 g/day to 500.0 g/day (Meharg et al., 2009).

Rice and beans make up 25% of the diet of the Brazilian population (IBGE, 2020). In Brazil, there are over ten popular dishes and desserts prepared with rice. The consumption of rice and beans is considered healthy compared with that of ultra-processed food, which are formulations of ingredients, created by series of industrial techniques and processes, such as packaged snacks, pre-prepared meat, pasta and pizza dishes, and others (Monteiro, 2019). Rice and beans are rich in nutrients and calories, and their consumption can guarantee the daily ingestion of 50% of the recommended daily water intake. In Brazil, rice is also less expensive than is ultra-processed food and is accessible for people of all socioeconomic levels (Ministry of Health, 2014). Approximately 83% of the Brazilian population consumes white rice, and about 4% consumes brown rice (IBGE, 2020). Given that the current population of Brazil is approximately 211 million, the population exposed to iAs in white and brown rice could be approximately 175 million and 8.4 million people, respectively.

The risk of consuming white rice is higher than is that of consuming brown rice, which is attributed to the lower concentration of iAs in brown rice. The Dietary Guidelines for the Brazilian Population established by the BNMH recommend the consumption of brown rice, rather than white rice, because of the composition, in terms of micronutrients and dietary fiber, of the former (Ministry of Health, 2014). Jo and Todorov (2019) reported that, as a result of the polishing process, white rice contains lower concentrations of phosphorus, potassium, manganese, and iron than does brown rice. Considering the results of the present risk assessment, we could conclude that brown rice is also a better option for human health. However, the sample size in this study does not allow for the conclusion that all Brazilian brown rice has less iAs than white rice. Further investigations of iAs in Brazilian rice are needed, given that the levels of arsenic in rice vary according to soil properties, type of irrigation, plant characteristics, and other factors.

Brown rice is typically reported to contain higher levels of arsenic than does white rice, because the arsenic is mainly stored in the external layers of the grain, which are partially removed when the grain is polished (Meharg and Raab, 2010; Yim et al., 2017). However, in the present study, the iAs concentration was found to be slightly lower in brown rice than in white rice, as confirmed by a hypothesis test (t-test, 95% confidence interval). The samples of brown and white rice came from different locations, and iAs concentration in rice can vary considerably according to the region of origin (Althobiti et al., 2018).

3.2. Non-cancer risk of exposure to iAs in rice

The results of our analysis of the non-cancer risks of exposure to iAs in white and brown rice in Brazil, estimated by calculating the fractional HQ by age and the lifetime HQ, are presented in Table 2. The fractional and lifetime HQ for white and brown rice consumption were below 1 for individuals of all ages. The lifetime HQ found is 3.02 $x10^{-1}$ for white rice, and 1.21 $x10^{-2}$.for brown rice. An HQ above 1 indicates that the dose ingested is higher than the reference dose and that there is a potential for adverse effects, in this context including cardiovascular and dermal effects (U.S. EPA, 2001).

Table 2 – Estimated fractional hazard quotients by age and hazard quotient for a lifetime for exposure to inorganic arsenic in polished (white) and husked (brown) rice.

	White rice		Brown rice	
	Hazard quotient		Hazard quotient	
Age (years)	Mean	95th percentile	Mean	95th percentile
< 1	3.60×10^{-03}	6.15×10^{-03}	1.44×10^{-04}	2.04×10^{-04}
1	2.04×10^{-02}	3.48×10^{-02}	8.15×10^{-04}	1.16×10^{-03}
2	1.64×10^{-02}	2.80×10^{-02}	6.55×10^{-04}	9.30×10^{-04}
3	1.60×10^{-02}	2.74×10^{-02}	6.41×10^{-04}	9.09×10^{-04}
4	1.56×10^{-02}	2.66×10^{-02}	6.22×10^{-04}	1.44×10^{-04}
5	1.22×10^{-02}	2.09×10^{-02}	4.89×10^{-04}	1.13×10^{-04}
6	1.13×10^{-02}	1.93×10^{-02}	4.51×10^{-04}	1.04×10^{-04}
7	1.00×10^{-02}	1.71×10^{-02}	4.00×10^{-04}	9.26×10^{-05}
8	9.03×10^{-03}	1.54×10^{-02}	3.61×10^{-04}	8.35×10^{-05}
9	7.90×10^{-03}	1.35×10^{-02}	3.16×10^{-04}	7.31×10^{-05}
10	5.89×10^{-03}	1.01×10^{-02}	2.35×10^{-04}	5.44×10^{-05}
11	5.22×10^{-03}	8.93×10^{-03}	2.09×10^{-04}	4.83×10^{-05}
12	4.62×10^{-03}	7.90×10^{-03}	1.85×10^{-04}	4.27×10^{-05}
13	4.18×10^{-03}	7.14×10^{-03}	1.67×10^{-04}	3.86×10^{-05}
14	3.89×10^{-03}	6.64×10^{-03}	1.55×10^{-04}	3.60×10^{-05}
15	3.63×10^{-03}	6.20×10^{-03}	1.45×10^{-04}	3.35×10^{-05}
16	3.50×10^{-03}	5.99×10^{-03}	1.40×10^{-04}	3.24×10^{-05}
17	3.39×10^{-03}	5.79×10^{-03}	1.35×10^{-04}	3.13×10^{-05}
18	3.30×10^{-03}	5.63×10^{-03}	1.32×10^{-04}	3.05×10^{-05}
19	3.33×10^{-03}	5.70×10^{-03}	1.33×10^{-04}	3.08×10^{-05}
20 to <25	1.60×10^{-02}	2.73×10^{-02}	6.39×10^{-04}	1.48×10^{-04}
25 to <30	1.53×10^{-02}	2.61×10^{-02}	6.11×10^{-04}	1.41×10^{-04}
30 to <35	1.50×10^{-02}	2.57×10^{-02}	6.00×10^{-04}	1.39×10^{-04}
35 to <45	2.96×10^{-02}	5.06×10^{-02}	1.18×10^{-03}	2.74×10^{-04}
45 to <55	2.93×10^{-02}	5.01×10^{-02}	1.17×10^{-03}	2.71×10^{-04}
55 to <65	2.71×10^{-02}	4.64×10^{-02}	1.08×10^{-03}	2.51×10^{-04}
65 to <75	6.39×10^{-03}	1.09×10^{-02}	2.56×10^{-04}	5.91×10^{-05}
0 to <70	3.02×10^{-01}	5.16×10^{-01}	1.21×10^{-02}	2.79×10^{-03}

Some studies have found HQ values above 1 for exposure to iAs in rice. In a study involving adults in Saudi Arabia, Al-Saleh et al. (2017) found an HQ of 1.2 (SD=0.4) for exposure to iAs in white rice. The authors assumed a daily rice consumption of 160 g/day to calculate the dose, and used the reference dose established by the EPA, as was used in the present study. In India, where arsenic in rice is a public health problem in some regions, Upadhyay et al. (2019) estimated an HQ above 1 for all age groups and a correlation test suggested that the risk of arsenic poisoning is higher among infants and children than among adults. In a study conducted in Taiwan, Chen et al. (2016) found an HQ below 1 for all individuals ≤ 65 years of age, (between 0.08 and 0.3) although they adopted a 5-fold higher reference dose of 0.015 mg/kg per day. The same RfD was adopted by Lin et al. (2015), which conducted a study of the non-cancer risk of exposure to total arsenic in rice for adults in 14 cities in China and found HQ values below 1 for all of the cities, between 0.07 and 0.3. In Punjab, India, Sharma et al. (2020) found an HQ of 0.45 for exposure to total arsenic in specific rice varieties and an exposure period of 70 years, using the RfD proposed by EPA.

3.3. Exposure to As in drinking water

The mean concentrations of total As in drinking water in the 2014–2018 period, for Brazil as a whole and for each of the main regions of the country, are shown in Table S.4. For the country as a whole, the mean concentration was below the MCL recommended by the BNMH (10 ng ml^{-1}), which is the same as that recommended by WHO (Ministry of Health, 2011; WHO, 2011).

The concentration of iAs in drinking water in Brazil ranged from 0.015 ng ml^{-1} to 13.0 ng ml^{-1}. In a high proportion of the samples (56.9%), the concentration was below the detection limit (censored data), and the proportion of samples in which the concentration was above the MCL was highest (8.8%) in the central-west region, as was the proportion of censured data. The greatest number of samples were collected in the southeastern region, which accounted for 68% of the total of samples. Among the samples collected in the northern region, there were none with an As concentration above the MCL. However, the number of samples collected was lower in the northern region than in the other regions, and samples were collected from only two of the seven states of the region. Therefore, the samples were probably not representative of the water quality of the region.

There were significant differences among the regions of the country in terms of the data quality. According to Brazilian law, the operators of the water treatment plants must collect and analyze samples of drinking water at least twice a year. However, small municipalities find it difficult to comply with that law, because of technical limitations, the cost of analysis, or a lack of accredited laboratories in the region (Brandt et al., 2019).

In Brazil, the presence of iAs in drinking water is restricted to just a few areas, although it is present in high concentrations in some of those areas. In some areas, such as the Amazon region, the sources of iAs are mainly past mining activities, whereas in other areas, such as the Quadrilátero Ferrífero and Ribeira Valley, both in the southeastern region, the sources include not only past mining activities but also the natural occurrence of arsenic in soil and groundwater (Borba et al., 2004; Costa et al., 2015; Figueiredo et al., 2007; Sakuma et al., 2010). In the southeastern Brazilian state of Minas Gerais, the mean concentrations of iAs in piped drinking water and well water were 0.21 ± 0.01 ng ml^{-1} and 1.34 ± 3.12 ng ml^{-1}, respectively, both lower than the mean values for Brazil and the southeastern region as a whole (Table S.4), which might be attributed to local features (Brandt et al., 2019; Ciminelli et al., 2017).

In Pakistan, the levels of iAs in groundwater were found to be high (1.5–201.0 ng ml^{-1}), being above the MCL established by the WHO in 62% of the samples (Lin et al., 2015). In Bangladesh, Rahman et al. (2013) found the total arsenic concentration in groundwater used for drinking to be 328 ng ml^{-1}. Despite the fact that those authors considered total arsenic, the levels were considered high, and the concentration of iAs would probably be above MCL established by the WHO. Similarly, in two villages in the state of West Bengal, India, the concentrations of total arsenic in groundwater were reported to be 124.5 ng ml^{-1} and 138.2 ng ml^{-1}, respectively (Upadhyay et al., 2019).

3.4. Risk of iAs in drinking water

Table 3 shows the estimated cancer risk by age and the ILCR for exposure to total As in drinking water, together with the ILCR for combined exposure to total As in drinking water and iAs in rice. The mean ILCR for exposure to total As in drinking water was 6.53×10^{-5} (95th percentile = 1.97×10^{-4}), lower than for exposure to iAs in white rice, albeit above the tolerable level of 1×10^{-5} proposed by the WHO (WHO, 2017b). Although, our results are overestimated, since iAs represents a fraction of total As. Drinking water represents approximately 32% of the risk for consumers of white rice and 90% of that for consumers of brown rice.

Ciminelli et al. (2017) conducted a cancer risk assessment for adults (18–74 years of age) consuming piped water and well water in the Brazilian state of Minas Gerais and found the risk to be 9×10^{-6} and 7×10^{-5}, respectively. Although those authors found concentrations of iAs in the piped and well water that were lower than those observed in our study, the mean risk associated with the consumption of well water was slightly higher than our 6.53×10^{-5} estimate. That might be due to the parameters they used to estimate the dose, because they considered a daily consumption of water of 2 L/day, resulting in a higher dose.

Table 3 – Estimated cancer risk and incremental lifetime cancer risk associated with exposure to arsenic in drinking water alone, as well as in drinking water combined with polished (white) rice and in drinking water combined with husked (brown) rice.

	Drinking water alone		Drinking water + white rice		Drinking water + brown rice	
Age (years) and ILCR	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile
< 1	1.35×10^{-06}	4.07×10^{-06}	3.0×10^{-06}	6.0×10^{-06}	1.4×10^{-06}	4.3×10^{-06}
1	1.21×10^{-06}	3.65×10^{-06}	1.0×10^{-05}	1.7×10^{-05}	1.6×10^{-06}	4.2×10^{-06}
2	1.39×10^{-06}	4.21×10^{-06}	8.8×10^{-06}	1.5×10^{-05}	1.7×10^{-06}	4.7×10^{-06}
3	1.02×10^{-06}	3.08×10^{-06}	8.3×10^{-06}	1.4×10^{-05}	1.3×10^{-06}	3.5×10^{-06}
4	1.02×10^{-06}	3.08×10^{-06}	8.1×10^{-06}	1.3×10^{-05}	1.3×10^{-06}	3.5×10^{-06}
5	1.02×10^{-06}	3.08×10^{-06}	6.6×10^{-06}	1.1×10^{-05}	1.3×10^{-06}	3.4×10^{-06}
6	9.29×10^{-07}	2.80×10^{-06}	6.0×10^{-06}	1.0×10^{-05}	1.2×10^{-06}	3.1×10^{-06}
7	9.29×10^{-07}	2.80×10^{-06}	5.5×10^{-06}	9.1×10^{-06}	1.1×10^{-06}	3.1×10^{-06}
8	9.29×10^{-07}	2.80×10^{-06}	5.0×10^{-06}	8.4×10^{-06}	1.1×10^{-06}	3.1×10^{-06}
9	9.29×10^{-07}	2.80×10^{-06}	4.5×10^{-06}	7.6×10^{-06}	1.1×10^{-06}	3.1×10^{-06}
10	9.29×10^{-07}	2.80×10^{-06}	3.6×10^{-06}	6.2×10^{-06}	1.1×10^{-06}	3.0×10^{-06}
11	5.57×10^{-07}	1.68×10^{-06}	2.9×10^{-06}	4.9×10^{-06}	6.7×10^{-07}	1.9×10^{-06}
12	5.57×10^{-07}	1.68×10^{-06}	2.7×10^{-06}	4.5×10^{-06}	6.6×10^{-07}	1.8×10^{-06}
13	5.57×10^{-07}	1.68×10^{-06}	2.5×10^{-06}	4.1×10^{-06}	6.5×10^{-07}	1.8×10^{-06}
14	5.57×10^{-07}	1.68×10^{-06}	2.3×10^{-06}	3.9×10^{-06}	6.4×10^{-07}	1.8×10^{-06}
15	5.57×10^{-07}	1.68×10^{-06}	2.2×10^{-06}	3.8×10^{-06}	6.4×10^{-07}	1.8×10^{-06}
16	5.57×10^{-07}	1.68×10^{-06}	2.2×10^{-06}	3.7×10^{-06}	6.4×10^{-07}	1.8×10^{-06}
17	5.57×10^{-07}	1.68×10^{-06}	2.1×10^{-06}	3.6×10^{-06}	6.3×10^{-07}	1.8×10^{-06}
18	5.57×10^{-07}	1.68×10^{-06}	2.1×10^{-06}	3.6×10^{-06}	6.3×10^{-07}	1.8×10^{-06}
19	5.57×10^{-07}	1.68×10^{-06}	2.1×10^{-06}	3.6×10^{-06}	6.3×10^{-07}	1.8×10^{-06}
20 to <25	4.27×10^{-06}	1.29×10^{-05}	1.2×10^{-05}	2.2×10^{-05}	4.7×10^{-06}	1.4×10^{-05}
25 to <30	4.64×10^{-06}	1.40×10^{-05}	1.2×10^{-05}	2.2×10^{-05}	5.1×10^{-06}	1.5×10^{-05}
30 to <35	5.11×10^{-06}	1.54×10^{-05}	1.2×10^{-05}	2.3×10^{-05}	5.5×10^{-06}	1.6×10^{-05}
35 to <45	1.02×10^{-05}	3.08×10^{-05}	2.4×10^{-05}	4.7×10^{-05}	1.1×10^{-05}	3.3×10^{-05}
45 to <55	1.07×10^{-05}	3.23×10^{-05}	2.4×10^{-05}	4.8×10^{-05}	1.2×10^{-05}	3.4×10^{-05}
55 to <65	1.11×10^{-05}	3.37×10^{-05}	2.4×10^{-05}	4.8×10^{-05}	1.2×10^{-05}	3.6×10^{-05}
65 to <70	2.55×10^{-06}	7.71×10^{-06}	5.5×10^{-06}	1.1×10^{-05}	2.7×10^{-06}	8.1×10^{-06}
ILCR	6.53×10^{-05}	1.97×10^{-04}	2.0×10^{-04}	3.6×10^{-04}	7.3×10^{-05}	2.1×10^{-04}

ILCR: incremental lifetime cancer risk.

The estimated fractional HQ and lifetime HQ values for exposure to total As in drinking water and for combined exposure to total As in drinking water and rice are shown in Table 4.

Table 4 – Estimated fractional hazard quotients by age and hazard quotient for a lifetime for exposure to inorganic arsenic in drinking water, as well as the fractional hazard indices by age and hazard index quotient for a lifetime for exposure to inorganic arsenic in drinking water combined with polished (white) rice and in drinking water combined with husked (brown) rice.

	Drinking water		Drinking water + white rice		Drinking water + brown rice	
	Hazard quotient		Hazard index		Hazard index	
Age (years)	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile
< 1	3.00×10^{-03}	8.87×10^{-03}	6.64×10^{-03}	1.31×10^{-02}	3.18×10^{-03}	9.18×10^{-03}
1	2.69×10^{-03}	7.95×10^{-03}	2.31×10^{-02}	3.83×10^{-02}	3.54×10^{-03}	8.89×10^{-03}
2	3.11×10^{-03}	9.17×10^{-03}	1.95×10^{-02}	3.25×10^{-02}	3.80×10^{-03}	9.96×10^{-03}
3	2.28×10^{-03}	6.73×10^{-03}	1.83×10^{-02}	3.04×10^{-02}	2.95×10^{-03}	7.47×10^{-03}
4	2.28×10^{-03}	6.73×10^{-03}	1.79×10^{-02}	2.96×10^{-02}	2.93×10^{-03}	7.46×10^{-03}
5	2.28×10^{-03}	6.73×10^{-03}	1.45×10^{-02}	2.42×10^{-02}	2.80×10^{-03}	7.32×10^{-03}
6	2.07×10^{-03}	6.12×10^{-03}	1.34×10^{-02}	2.22×10^{-02}	2.55×10^{-03}	6.66×10^{-03}
7	2.07×10^{-03}	6.12×10^{-03}	1.21×10^{-02}	2.02×10^{-02}	2.50×10^{-03}	6.61×10^{-03}
8	2.07×10^{-03}	6.12×10^{-03}	1.11×10^{-02}	1.86×10^{-02}	2.46×10^{-03}	6.57×10^{-03}
9	2.07×10^{-03}	6.12×10^{-03}	9.99×10^{-03}	1.68×10^{-02}	2.41×10^{-03}	6.53×10^{-03}
10	2.07×10^{-03}	6.12×10^{-03}	7.98×10^{-03}	1.36×10^{-02}	2.33×10^{-03}	6.45×10^{-03}
11	1.24×10^{-03}	3.67×10^{-03}	6.48×10^{-03}	1.09×10^{-02}	1.47×10^{-03}	3.94×10^{-03}
12	1.24×10^{-03}	3.67×10^{-03}	5.88×10^{-03}	9.87×10^{-03}	1.44×10^{-03}	3.91×10^{-03}
13	1.24×10^{-03}	3.67×10^{-03}	5.43×10^{-03}	9.17×10^{-03}	1.42×10^{-03}	3.90×10^{-03}
14	1.24×10^{-03}	3.67×10^{-03}	5.14×10^{-03}	8.74×10^{-03}	1.41×10^{-03}	3.89×10^{-03}
15	1.24×10^{-03}	3.67×10^{-03}	4.89×10^{-03}	8.33×10^{-03}	1.40×10^{-03}	3.87×10^{-03}
16	1.24×10^{-03}	3.67×10^{-03}	4.76×10^{-03}	8.14×10^{-03}	1.40×10^{-03}	3.87×10^{-03}
17	1.24×10^{-03}	3.67×10^{-03}	4.64×10^{-03}	7.95×10^{-03}	1.39×10^{-03}	3.87×10^{-03}
18	1.24×10^{-03}	3.67×10^{-03}	4.55×10^{-03}	7.84×10^{-03}	1.39×10^{-03}	3.86×10^{-03}
19	1.24×10^{-03}	3.67×10^{-03}	4.59×10^{-03}	7.88×10^{-03}	1.39×10^{-03}	3.86×10^{-03}
20 to <25	9.52×10^{-03}	2.81×10^{-02}	2.56×10^{-02}	4.73×10^{-02}	1.03×10^{-02}	2.93×10^{-02}
25 to <30	1.04×10^{-02}	3.06×10^{-02}	2.58×10^{-02}	4.87×10^{-02}	1.11×10^{-02}	3.18×10^{-02}
30 to <35	1.14×10^{-02}	3.36×10^{-02}	2.65×10^{-02}	5.12×10^{-02}	1.21×10^{-02}	3.49×10^{-02}
35 to <45	2.28×10^{-02}	6.73×10^{-02}	5.26×10^{-02}	1.02×10^{-01}	2.42×10^{-02}	6.97×10^{-02}
45 to <55	2.38×10^{-02}	7.03×10^{-02}	5.34×10^{-02}	1.05×10^{-01}	2.53×10^{-02}	7.28×10^{-02}
55 to <65	2.48×10^{-02}	7.34×10^{-02}	5.23×10^{-02}	1.05×10^{-01}	2.62×10^{-02}	7.58×10^{-02}
65 to <70	5.69×10^{-03}	1.68×10^{-02}	1.22×10^{-02}	2.43×10^{-02}	6.02×10^{-03}	1.74×10^{-02}
0 to <70	1.46×10^{-01}	4.30×10^{-01}	4.49×10^{-01}	7.96×10^{-01}	1.59×10^{-01}	4.50×10^{-01}

The fractional HQ values and lifetime HQ for exposure to total As in water were below 1, suggesting that non-cancer effects resulting from this exposure are unlikely. The same were observed for fractional hazard index (HI) and lifetime HI, which is the sum of the fractional HQs or lifetime HQs for exposure to water and rice.

In a study conducted in three regions of Pakistan, Lin et al. (2015) estimated the HQ for exposure to iAs in drinking water, with an exposure duration of 67 years, and found it to be above 1 (11.01 and 3.84), much higher than the values found in the present study, in two regions and below 1 (0.85) in one. In some regions, such as Bangladesh and West Bengal, India, where the drinking water supplies naturally have high levels of iAs, groundwater is the main source of exposure to iAs (WHO, 2011). Our results indicate that, in Brazil, white rice is a more significant source of iAs exposure and risk than is drinking water.

3.5. Exposure to iAs in rice

In the present study, the mean concentration of iAs in white rice was found to be 100.1 ± 44.62 ng g^{-1}, which is lower than the MCL of 300 ng g^{-1} proposed by the BNMH for total arsenic (Ministry of Health, 2013). That value is also lower than the MCL of 200 ng g^{-1} for iAs established by the Joint FAO/WHO Codex Committee on Contaminants in Foods (Joint FAO/WHO, 2018), European Commission (EC, 2015) and Chinese Ministry of Health (Ministry of Health of China, 2014). Among the 64 samples of white rice evaluated in the present study, the concentration of iAs was above the FAO/WHO MCL (ranging from 200 ng g^{-1} to 220 ng g^{-1} and thus in accordance with Brazilian MCL) in only 4 samples. Similar iAs concentrations have been found in other countries, including the United States and China. According to the FDA (U.S. FDA, 2016), the weighted mean concentration of iAs in 429 samples of different types of white rice based on the relative market-share estimates in the United States is 92.3 ng g^{-1} (standard error, 1.3). Considering different grain sizes, the mean concentration of iAs was 102.0 ng g^{-1} for long grain rice (n = 173), 81.5 ng g^{-1} for medium grain rice (n = 94), and 78.9 ng g^{-1} for short grain rice (n = 23). Similarly, in China, where rice is a staple food, Li et al. (2011) reported an iAs concentration of 103.0 ng g^{-1} in 151 samples of white rice from published studies. Nevertheless, higher iAs concentrations, ranging from 290.0 ng g^{-1} to 950.0 ng g^{-1}, exceeding the WHO MCL and more than 9 times higher than the mean concentration found in our study, were found in white rice samples from India (Upadhyay et al., 2019). Lower levels were found in white rice from Taiwan, where rice is the primary staple food, the mean iAs concentration being 65.9 ng g^{-1} in 51 samples (Chen et al., 2016), and from Iran, a rice-producing country, the mean iAs concentration in 15 samples being 82.0 ng g^{-1} (Cano-Lamadrid et al., 2015).

In Brazil, only a few studies have evaluated the concentration of iAs in white rice. One study assessed white rice purchased in local markets in the state of Minas Gerais, in the southeastern region of the country, and found an iAs concentration of 102.0 ng g^{-1} (Ciminelli et al., 2017), comparable to that observed in the present study. Cerveira et al. (2015) reported a mean iAs concentration of 94.2 ± 39.5 ng g^{-1} (range, 54.0–150.0 ng g^{-1}; n = 7), similar to our findings. Also, in the state of Minas Gerais, Corguinha et al. (2015) found low concentrations of total arsenic, below the detection limit of 15.0 ng g^{-1}, which was attributed to a low concentration of arsenic in soil. In the present study, we have access to data of three samples from Minas Gerais and found iAs concentrations ranging from 105.0 ng g^{-1} to 132.0 ng g^{-1}, higher than the values reported in either of the studies cited above (Batista et al., 2015).

In the present study, the mean concentration of iAs in brown rice was found to be 80.1 ± 55.5 ng g^{-1}. In Brazil, the MCL is the same (300.0 ng g^{-1}) for brown and white rice, although the Joint FAO/WHO Codex Committee on Contaminants in Foods recommends an MCL of 350.0 ng g^{-1} for brown rice (Joint FAO/WHO, 2016). Higher mean concentrations of iAs were found in brown rice from Taiwan (Chen et al., 2016): 103.9 ± 45.0 ng g^{-1} for arsenate and 2.2 ± 1.2 ng g^{-1} for mobile arsenite (n = 13). The U.S. FDA (2016) reported a mean iAs concentration in brown rice of 156.5 ng g^{-1} (range, 34.0–249.0 ng g^{-1}), in 120 samples, as well as reporting a mean iAs concentration in 144 samples of jasmine, basmati, parboiled, and pre-cooked brown rice of 153.8 ± 3.2 ng g^{-1}. In contrast, Fu et al. (2011) reported a mean predicted concentration of iAs in 282 samples of brown rice from Hainan, an island in China, of 57.0 ng g^{-1}, even lower than the concentration found in our study. That concentration was considered lower than or similar to that reported for other regions of China, which the authors suggested was attributed to soil properties (organic matter, phosphorus content, humic acid, and iron-manganese) and arsenic speciation in soil.

Other studies conducted in Brazil have reported concentrations of iAs in brown rice higher than those adopted in the present study, reported by Batista et al. (2015). Cerveira et al. (2015) found concentrations ranging from 88.0 ng g^{-1} to 163.0 ng g^{-1} (n = 4), with a mean value of 131.0 ± 32.0 ng g^{-1}. Batista et al. (2011) reported a mean iAs concentration of 188 ng g^{-1} (range, 176.0–202.0 ng g^{-1}) in samples of brown rice from the states of Rio Grande do Sul and São Paulo. Kato et al. (2019) found significant variation in the levels of total arsenic in brown rice f from the states of Rio Grande do Sul (235.0 ± 157.0 ng g^{-1}), Santa Catarina (157.0 ± 108.0 ng g^{-1}), and Mato Grosso (4.0 ± 2.0 ng g^{-1}), which was attributed to differences in water management and local features.

The concentration of iAs in rice can vary according to the presence of arsenic in soil or in water used for irrigation, natural or otherwise (Dittmar et al., 2010); the current or past use of pesticides containing arsenic; anthropogenic sources of iAs, such as mining or industrial activities, near the rice paddies (Joint FAO/WHO, 2017); water management (Moreno-Jiménez et al., 2014); and rice variety (Duan et al., 2017; Sommella et al., 2013). In Brazil, some studies have identified significant variation in iAs concentrations and other non-essential elements in rice, even among rice grains from the same producer. Rice variety, microclimatic conditions, and geochemical properties are reported to be major factors affecting iAs concentration in rice (Monteiro et al., 2020; Segura et al., 2020). Many of those factors can be associated with the location of the rice field (Althobiti et al., 2018). Therefore, we conducted an analysis based on the location where the samples were collected, although we have that information only for the samples of brown rice obtained directly from farms. The samples of white rice were all obtained from markets, and the specific cultivation location was not noted on any of the labels (Batista et al., 2015).

Figure S1 shows a box plot of iAs concentrations in brown rice by cities where the farms were located (Batista et al., 2015). Only cities with more than two samples were included, resulting in three of eight cities. The mean iAs concentration in samples from City 1 was 64.0 ± 19.0 ng g^{-1} (n = 9), from City 2 was 45.1 ± 43.0 ng g^{-1} (n = 30), and from City 3 was 79.8 ± 22.0 ng g^{-1} (n = 14). City 2 presented the highest variation, but on average the three locations produced rice with concentration of iAs under 100 ng g^{-1}. suggesting that the studied farms produced rice with low concentration of iAs.

Figure 2 shows a box plot of iAs concentrations in brown rice by the origin of the samples (farms or markets), which were similarly processed (Batista et al., 2015).

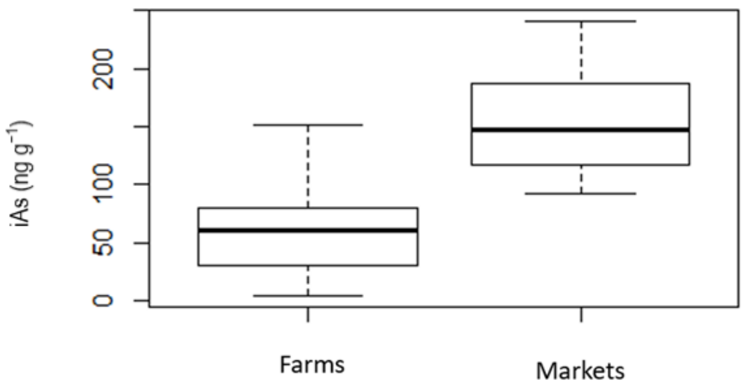

Fig. 2. Box plot of inorganic arsenic concentrations in husked (brown) rice from farms and markets.

The mean concentration of iAs for the samples obtained from markets (n = 21) of 154.91 ± 44.8 ng g^{-1} (range, 135.7–222.8 ng g^{-1}) was similar to that reported in the literature, but much higher than the 57.36 ± 34.6 ng g^{-1} (range, 45.1–79.7 ng g^{-1}) estimate from the samples obtained from farms (n = 69). That discrepancy influenced the overall mean iAs concentration in the data set for brown rice. The farms where the brown rice was cultivated are located in two states in the southern region of Brazil—Rio Grande do Sul and Santa Catarina—the two main rice-producing states in the country, accounting for approximately 69% and 9% of the national rice production, respectively (Conab, 2015). Of the brown rice samples purchased in markets, most were produced in Rio Grande do Sul or São Paulo, although the labels did not identify the specific cities, and 12 of the samples had labels that provided no information regarding the state in which the rice was grown. Possible explanations for the lower iAs concentrations in brown rice obtained from farms include the location and management of the farms, which receive support from the Brazilian Agency for Agricultural Research, a governmental agency linked to the Ministry of Agriculture, Livestock, and Food Supply. The mission of the agency is to improve agriculture practices, and one of its goals is to achieve food safety and food security, providing support for farmers to produce more food and food free of hazardous substances (Ministry of Agriculture, 2019). Adopting good agriculture practices, such as avoiding contamination sources and implementing water management, as well as monitoring soil and water quality, could indirectly result in lower iAs concentrations in rice.

Water management can influence arsenic concentration in rice. Rice cultivated under flooded conditions absorbs more arsenic than does that cultivated in unsaturated soils, while also absorbing less cadmium from soil (Moreno-Jiménez et al., 2014). Silva et al. (2020) evaluated the iAs concentration in three different varieties of rice cultivated under different water conditions and during different phases of development. They found that water management had the greatest impact on iAs concentration during the reproductive period, in which cultivation in unsaturated soils resulted in the lowest arsenic accumulation in rice grains, as well as the highest accumulation of cadmium and lead. Both were below the acceptable levels established by the FAO/WHO (Joint FAO/WHO, 2018).

In the southern region of Brazil, rice is usually cultivated in flooded fields. However, we hypothesized that rice farmers could be cultivating rice in unsaturated soils, which could explain the low concentration of iAs in rice, although it would also result in higher cadmium concentrations. Using cadmium concentration as an indicator, we found no linear correlation between arsenic and cadmium concentration in brown rice from farms ($r = 0.049$; $p = 0.690$), so there is no evidence that the rice was grown in unsaturated soils. Therefore, the low concentration of iAs is probably attributable to other factors.

Some types of fertilizers, pesticides, and soil acidity correctors, such as limestone, can be a source of arsenic in the environment. In terms of pesticides, Segura et al (2016) evaluated rice samples from Brazil and identified that iAs was higher in organic rice than in conventional rice (45% higher for white rice, and 41% for brown rice), suggesting that pesticides were not increasing iAs concentrations. In another study conducted in Brazil, Avelar et al. (2016) analyzed samples of limestone, a natural unprocessed mineral, and found an arsenic concentration of 11.74 ± 1.42 µg g^{-1}, similar to values reported for limestone in the United States, where the U.S. FDA has declared it a major source of arsenic in the soil, posing risks for humans and animals (U.S. FDA, 2016). The anaerobic conditions in flooded fields favor pH correction, so no limestone is necessary. However, in some cases, rice seeds are sown directly onto dry soil, and the field is flooded 30 days later. Therefore, the recommended is to use limestone only once every five years (Ministry of Agriculture, 2007).

Phosphorus fertilizers also can be a source of arsenic in the environment. Avelar et al. (2016) evaluated samples of phosphorus fertilizers in Brazil and found concentrations of total arsenic similar to or even lower than those reported for other countries around the world—11.74 ± 1.42 µg g^{-1}. Those concentrations were below the MCL established for Brazil, although Brazilian soils demand more phosphorus fertilizers, because iron and aluminum are more likely to be adsorbed by soil particles than is phosphorus. In comparison with Europe, Brazil uses nearly 100 times more phosphorus fertilizer in agricultural fields (140 kg/ha). On average, 6.4 ± 1.2 g/ha of arsenic is added to the soil in Brazil every year. Although the arsenic concentrations in fertilizers do not pose a threat to human health in the short term, intensive medium- to long-term use of such fertilizers could lead to the accumulation of arsenic in soil, which can represent risks to human health, and soil monitoring is therefore necessary (Silva et al., 2017). In a study conducted in the state of São Paulo, Campos (2002) found that the intense use of phosphorus fertilizers for decades increased the soil concentrations of arsenic, as well as its mobility and availability, given that phosphorus, rather than arsenic, can be adsorbed by the soil. That increased the concentration of arsenic in groundwater and consequently in well water. In Rio Grande do Sul, the main rice-producing state in Brazil, contamination of soil and groundwater with arsenic, due to fertilizer factory activities, has been reported. In a study conducted in the Patos Lagoon Estuary, which is surrounded by rice paddies, Mirlean and Roisenberg (2006) reported arsenic concentration ranging from 7.5 µg g^{-1} to 27.5 µg g^{-1} in soil, exceeding the local background value (1.02 µg g^{-1}), and from 1.23 µg g^{-1} to 25.45 ng ml^{-1} in water, also exceeding the local background value (0.14 ng ml^{-1}). The authors concluded that the soil and water contamination are a result of precipitation from factory emissions, over a period of more than 40 years, accumulating total arsenic in the superficial horizon of the soil. Most studies of arsenic in the environment of Brazil, including those conducted in the states of Espírito Santo, Bahia, Rio de Janeiro, Paraná, and São Paulo (Alves et al., 2014; Cagnin et al., 2017; Espinoza-Quiñones et al., 2015; Mirlean et al., 2014), have attributed it to industrial or mining activities, which do not typically occur near rice paddies.

3.6. Reducing the risk

The concentration of arsenic in rice grains depends on the arsenic concentration in soil, its bioavailability, and the rice genotype (cultivar). Because some rice cultivars reportedly store less arsenic, selecting those cultivars could be a good strategy when the soil is known to contain bioavailable arsenic (Batista et al., 2014). In a study conducted in Punjab, India, Sharma et al., (2020) investigated two rice varieties (PUSA1121 and PR122) and found that they may be suitable for cultivation in fields contaminated with arsenic. Another study conducted in India showed significant variability of arsenic concentration in five rice varieties (Upadhyay et al., 2019). In that study, the Ranjit variety showed a mean iAs concentration of 290 ± 0.021 ng g^{-1}, more than three times lower than the 950 ± 0.044 ng g^{-1} shown by the Gosai variety.

In the present study, we had information about brown rice varieties only for the samples of collected directly from farms (*i.e.*, not for those obtained from markets). Although there are four rice varieties, we had more than one sample for only two. The mean iAs concentration was 80.7 ± 22.35 ng g^{-1} for the Irga 424 variety (n = 19) and 46.6 ± 31.69 ng g^{-1} for the Puitá variety (n = 48), as shown in Figure 3. From a risk management perspective, it would be interesting to conduct further studies to determine whether the Puitá variety in fact stores less arsenic than do other varieties. Adopting this rice variety could be an easy, effective strategy to reduce health risks for the population.

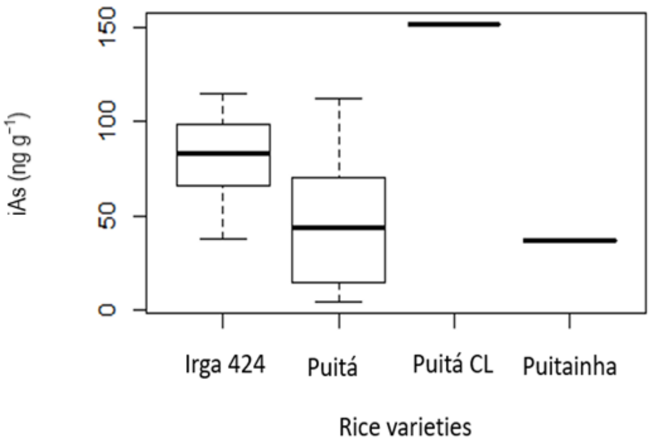

Fig. 3. Box plot of inorganic arsenic (iAs) concentrations in four rice varieties.

A number of measures for reducing the risk of iAs exposure associated with rice consumption have been proposed. Practices that can be adopted by the consumers, including rinsing, soaking, and some cooking methods, can remove part of the iAs. However, there are uncertainties regarding the effectiveness of such practices and the influence of the type of rice; in addition, the iAs content in the water used in cooking the rice can affect the final iAs concentration (Joint FAO/WHO, 2011; U.S. FDA, 2016).

Sengupta et al. (2006) reported that a method of washing and cooking rice, specific to India, removed up to 57% of the total arsenic from rice containing 203–540 ng g^{-1} of arsenic. Washing the rice approximately six times, until the water is clear, reduced the total arsenic concentration by approximately half, and cooking the rice at a rice-to-water ratio of 1:6, thereafter discarding the excess water, removed the remaining arsenic. A study conducted in Saudi Arabia showed that soaking rice for 20 min removed 98% of the total arsenic and that rinsing rice three times removed 97% (Al-Saleh and Abduljabbar, 2017). In a study conducted in Japan, Naito et al. (2015) observed that rinsing rice removed mainly iAs. Although rinsing and cooking practices can reduce the arsenic concentration in rice, such practices also reduce enriched iron, folate, thiamin, and niacin (U.S. FDA, 2016). One study showed that rinsing rice before cooking had a minimal effect on arsenic concentration, while removing nutrients such as enriched iron, folate, thiamin, and niacin. Cooking rice in excess water proved to be more effective in reducing the iAs concentration in rice, removing 40–60% depending on the type of rice, while reducing those same nutrients by 50–70% (Gray et al., 2016). Cooking the rice also can change the speciation of the arsenic to a form that is more toxic or less toxic, depending on the type of rice and its region of origin (Althobiti et al., 2018). Preliminary estimates indicate that the reduction in iAs in rice from rinsing and cooking practices in water containing low levels of arsenic (< 3 µg/L) ranges from 28% to 60%. Because there is substantial uncertainty in those estimates, there have been calls for further research to evaluate not only changes in total arsenic and iAs concentrations in rice but also the impact on nutritional content (U.S. FDA, 2016).

Nachman et al. (2018) proposed actions that stakeholders (regulators, food producers, researchers, and health professionals) could take at each step of the supply chain to reduce the risk associated with dietary exposure to iAs. Brazil is committed to the Sustainable Development Goals of the United Nations, one of which, End Hunger, also calls for food safety and sustainable agriculture (United Nations, 2015). Investments in research are essential to assess best practices for reducing iAs concentrations in rice, and public policies could provide support to rice producers through education and by promoting the adoption of good agriculture practices.

Pedron et al. (2019) evaluated polishing and washing rice for potential implementation in the food industry. Polishing the grain removed 13–54% of total arsenic, depending on the duration of the polishing, which ranged from 20 s to 60 s. In the case of brown rice, washing the grains removed approximately 38.8% of total arsenic. Jo and Todorov (2019) found that polishing brown rice can remove 16–33% of iAs. However, these practices are known to reduce some nutrients, as reported by Pedron et al. (2019), who found that washing and polishing rice reduced the concentrations of nutrients (manganese, iron, cobalt, copper, zinc, and selenium) by 33–95%.

Another potential arsenic mitigation strategy is using fungi from the rhizosphere of rice. Segura et al. (2018) tested two genera of fungi and obtained promising results. The authors concluded that direct application of *Aspergillus* sp. in soils might be a good alternative for reducing iAs concentration in rice grains.

The Joint FAO/WHO Code of Practice for the Prevention and Reduction of Arsenic Contamination in Rice states that national authorities should consider the implementation of measures directed at the sources of iAs and the adoption of specific agricultural practices. Authorities could determine which measures are most appropriate for their countries. Such measures include the identification and avoidance of arsenic sources: water for irrigation; contaminated soil; atmospheric emissions and wastewater from industry; materials used in agricultural and livestock production (pesticides, veterinary medicines, feed, soil amendments, and fertilizers); and waste from other materials (*e.g.*, timber treated with copper chrome arsenate). Specific agricultural measures include education programs for farmers, and implementing aerobic conditions or intermittent flooding during rice production, although only if cadmium concentrations in rice are not a concern (Joint FAO/WHO, 2017).

The results of the present risk assessment describe the estimates of the incidence of cancer in the Brazilian population, based on the application of EPA's cancer slope and exposure scenarios adopted. By changing the inputs of the Monte Carlo analysis, we can simulate the likely impact of mitigation strategies (FDA, 2016). We evaluated six different interventions aimed at reducing the cancer risk, calculating the risk for each of those interventions: scenario 1—consumption exclusively of brown rice from farms with low levels of iAs; scenario 2—consumption exclusively of brown rice of the Puitá variety, which was found to have the lowest iAs concentration (mean, 46.6 ng g^{-1}); scenario 3—adoption of a white rice MCL of 100 ng g^{-1}; scenario 4—adoption of a white rice MCL of 75 ng g^{-1}; scenario 5—adoption of a white rice MCL of 50 ng g^{-1}; and scenario 6—no consumption of white rice by infants and children ≤ 6 years of age (we chose white rice because it is the type of rice most widely consumed in Brazil). The U.S. FDA has proposed interventions similar to those evaluated here (U.S. FDA, 2016). To calculate the risk for those hypothetical scenarios, any samples above the proposed limit were removed. For scenarios 1 and 2, the complete data set was considered and the iAs limit was the maximum concentration found. Table 5 shows the parameters and the results of the risk assessment for each scenario.

Table 5

Estimated incremental lifetime cancer risk and parameters for hypothetical scenarios of interventions to reduce the cancer risk of exposure to inorganic arsenic in Brazil.

Scenario	iAs limit (ng g^{-1})	N	iAs concentration (ng g^{-1}) Mean; SD	Distribution (Mean; SD or μ; δ)	ILCR Mean	95th percentile	Reduction in ILCR (%)
1. Consumption of brown rice from farms with low iAs levels	151.9	69	57.36; 34.36	Log-normal (3.77; 0.87)	5.12×10^{-06}	7.23×10^{-06}	5.70
2. Consumption of brown rice of the Puitá variety	112	48	46.58; 31.68	Log-normal (3.51; 0.91)	4.81×10^{-06}	7.16×10^{-06}	11.38
3. Imposition of a white rice MCL of 100 ng g^{-1}	100	37	71.94; 22.47	Normal (71.94; 22.47)	9.83×10^{-05}	1.48×10^{-04}	27.93
4. Imposition of a white rice MCL of 75 ng g^{-1})	75	17	53.74; 21.15	Normal (53.74; 21.15)	7.41×10^{-05}	1.22×10^{-04}	45.63
5. Imposition of a white rice MCL of 50 ng g^{-1})	50	6	30.55; 16.85	Normal (30.55; 16.85)	4.39×10^{-05}	8.07×10^{-05}	67.82
6. No consumption of white rice ≤ 6 years of age	200	64	100.17; 44.62	Normal (100.17; 44.62)	1.01×10^{-04}	1.72×10^{-04}	26.09

iAs: inorganic arsenic; ILCR: incremental lifetime cancer risk; MCL: maximum contaminant level

There is no guideline establishing an acceptable level of risk associated with exposure to arsenic in food. Some studies have used the EPA guideline for contaminated areas, which established an acceptable cancer risk ranging from 10^{-4} to 10^{-6} (Al-Saleh and Abduljabbar, 2017; Sharma et al., 2020; Shibata et al., 2016). Scenario 2 presented the lowest ILCR, close to 10^{-6}., in which the MCL was 48 ng g^{-1}, more than 7 times lower than the MCL proposed by the FAO for white rice (Joint FAO/WHO, 2018). In this scenario there is a reduction of about 11% of the risk, compared with the risk of consuming brown rice. It is likely that polishing Puitá rice would further reduce the iAs content and consequently the risk.

Scenario 5 represents the adoption of an MCL of 50 ng g^{-1} for white rice, the kind of rice most widely consumed in Brazil, resulting in the highest decrease of ILCR, around 68% (compared with the risk from consumption of white rice) and third lowest ILCR. Excluding rice from the diet of infants and young children (scenario 6) is also a scenario proposed by the FDA (U.S. FDA, 2016), and it could reduce the ILCR by nearly 26%, although it would necessitate a substantial change in Brazilian culture, which is unlikely to happen. Daycare centers introduce rice into the diet of infants at four months of age, and that could be delayed, another type of food, also rich in nutrients and unprocessed, being prioritized. The ILCR for scenario 6 is similar to that of reducing the MCL to 100 ng g^{-1} (scenario 3). In this context, Segura et al. (2020) emphasized the need for crop-tracking, given that the iAs content in rice can vary significantly, even among samples from the same producer. That would allow the selection of grains with less iAs for consumption by vulnerable populations, such as infants and children.

There is a need for additional studies aimed at determining which mitigation strategies are the most suitable, taking into consideration the complexity of aspects related to agriculture, daycare centers, schools, maternity leave, and culture. The same interventions proposed in the risk assessment conducted by the U.S. FDA produced results that were less significant, possibly because rice consumption is lower in the United States than in Brazil, or because the dose–response model was different. In their risk assessment of exposure to iAs in rice (U.S. FDA, 2016), eliminating rice from the diet of infants and children ≤ 6 years of age would reduce the ILCR by 6%; imposing an MCL of 100 ng g^{-1} would reduce the ILCR by 4.3–18.3%; imposing an MCL of 75 ng g^{-1} would reduce the ILCR by 20–37%; and imposing an MCL of 50 ng g^{-1} would reduce the ILCR by 44.5%.

4. Conclusion

The ILCR, as well as the cancer risk for each age or age group, associated with exposure to white and brown rice in Brazil are high, even when the iAs concentration is under the MCLs proposed by the FAO/WHO and BNMH. That might be attributed to the high level of rice consumption in the country, and the MCL established by the BNMH does not seem to be appropriate in view of the exposure scenario. The risk is highest at 1–6 years of age, when rice consumption is high, given the lower body weight at that age, resulting in a higher dose of iAs and, consequently, a higher risk. The results are influenced by the exposure parameters adopted, and possibly to some uncertainties related to them. A more extensive exposure assessment is needed.

According to our findings, in Brazil, the risk associated with the consumption of brown rice appears to be lower than is that associated with the consumption of white rice, given that we found the iAs concentration to be lower in brown rice. It is possible that the brown rice studied would be polished and sold as white rice. Thus, we can only conclude that samples of rice from some farms presented a lower concentration of iAs, and it is not specific for brown rice. Further studies are needed to verify our finding that some farms are producing rice with a lower concentration of iAs and, if verified, to implement interventions based on that understanding. We found some evidence that this low concentration of iAs could be explained by the variety of rice and by the practices adopted in rice fields.

The non-cancer risk associated with exposure to rice in Brazil is not concerning. Cancer and non-cancer risks associated with exposure to drinking water are lower than the risk associated with exposure to iAs in white rice, although the cancer risk is considered to be above the tolerable level established in the WHO guidelines. More studies with data of iAs in drinking water from Brazil would be valuable to make a better estimation of the risk associated to exposure to drinking water.

The actual ILCR is probably higher than that found in this study, because we did not consider the presence of rice in other foods, such as infant cereal and formula. In addition, we presented some potentially efficient options for mitigating the risk, each of which could have social, political, and economic effects. Those effects should be evaluated in future studies.

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Supplementary material

Table S.1 – Parameters adopted for assessing the risk of exposure to inorganic arsenic in rice and drinking water.

		Rates of ingestion		
Age (years)	Body weight (kg)*	Rice (row) (g/day)**	Drinking water (L/day) Brandt et al. (2019)	Exposure duration (years)
< 1	7.82	9.0	0.23	0.75/0.50***
1	11.19	54.9	0.15	1.00
2	13.70	54.0	0.21	1.00
3	15.71	60.6	0.17	1.00
4	17.80	66.7	0.20	1.00
5	19.77	58.2	0.22	1.00
6	22.17	60.2	0.22	1.00
7	24.98	60.2	0.25	1.00
8	27.70	60.2	0.28	1.00
9	31.66	60.2	0.32	1.00
10	33.82	47.9	0.34	1.00
11	38.11	47.9	0.23	1.00
12	43.06	47.9	0.26	1.00
13	47.66	47.9	0.29	1.00
14	51.21	47.9	0.31	1.00
15	54.87	47.9	0.33	1.00
16	56.82	47.9	0.34	1.00
17	58.79	47.9	0.35	1.00
18	60.38	47.9	0.36	1.00
19	61.18	49.1	0.37	1.00
20 to <25	63.77	49.1	0.59	5.00
25 to <30	66.70	49.1	0.67	5.00
30 to <35	67.95	49.1	0.75	5.00
35 to <45	68.94	49.1	0.76	10.00
45 to <55	69.54	49.1	0.80	10.00
55 to <65	68.93	45.0	0.83	10.00
65 to <70	66.52	40.9	0.73	10.00

* (IBGE, 2010)

** (IBGE, 2020; Leroux et al., 2018; São Paulo, 2011a; São Paulo, 2011b).

* According to the São Paulo Municipal Department of Education guidelines for food consumption at daycare centers, infants should not be fed rice until 4 months of age (São Paulo, 2011a); and the WHO recommends that infants start to drink water at 6 months of age (UNICEF-WHO-UNESCO, 2010).

Table S.2 – Descriptive statistics for inorganic arsenic (iAs) concentrations in samples of polished (white) and husked (brown) rice.

Statistic	White rice (n = 64) (ng g^{-1})	Brown rice (n = 90) (ng g^{-1})
Mean	100.17	80.12
95% CI	89.02 – 111.31	68.49 – 91.76
Median	94.85	72.54
Standard deviation	44.62	55.56
Variation	1991.24	3086.95
Minimum	4.30	4.26
Maximum	228.70	240.89

Table S.3 – Estimated average daily dose (mg/kg-day) associated with exposure to inorganic arsenic in polished (white) and husked (brown) rice and drinking water.

Age (years)	White rice		Brown rice		Drinking water	
	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile
< 1	1.01×10^{-04}	1.72×10^{-04}	4.01×10^{-06}	5.67×10^{-06}	1.25×10^{-04}	3.77×10^{-04}
1	4.28×10^{-04}	7.31×10^{-04}	1.70×10^{-05}	2.41×10^{-05}	5.59×10^{-05}	1.69×10^{-04}
2	3.44×10^{-04}	5.88×10^{-04}	1.37×10^{-05}	1.94×10^{-05}	6.46×10^{-05}	1.95×10^{-04}
3	3.36×10^{-04}	5.75×10^{-04}	1.34×10^{-05}	1.90×10^{-05}	4.73×10^{-05}	1.43×10^{-04}
4	3.27×10^{-04}	5.59×10^{-04}	1.30×10^{-05}	1.84×10^{-05}	4.73×10^{-05}	1.43×10^{-04}
5	2.57×10^{-04}	4.39×10^{-04}	1.02×10^{-05}	1.45×10^{-05}	4.73×10^{-05}	1.43×10^{-04}
6	2.37×10^{-04}	4.05×10^{-04}	9.43×10^{-06}	1.33×10^{-05}	4.30×10^{-05}	1.30×10^{-04}
7	2.10×10^{-04}	3.59×10^{-04}	8.37×10^{-06}	1.18×10^{-05}	4.30×10^{-05}	1.30×10^{-04}
8	1.90×10^{-04}	3.24×10^{-04}	7.55×10^{-06}	1.07×10^{-05}	4.30×10^{-05}	1.30×10^{-04}
9	1.66×10^{-04}	2.84×10^{-04}	6.60×10^{-06}	9.34×10^{-06}	4.30×10^{-05}	1.30×10^{-04}
10	1.24×10^{-04}	2.11×10^{-04}	4.92×10^{-06}	6.96×10^{-06}	4.30×10^{-05}	1.30×10^{-04}
11	1.10×10^{-04}	1.88×10^{-04}	4.37×10^{-06}	6.18×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
12	9.70×10^{-05}	1.66×10^{-04}	3.86×10^{-06}	5.47×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
13	8.77×10^{-05}	1.50×10^{-04}	3.49×10^{-06}	4.94×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
14	8.16×10^{-05}	1.40×10^{-04}	3.25×10^{-06}	4.60×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
15	7.61×10^{-05}	1.30×10^{-04}	3.03×10^{-06}	4.29×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
16	7.35×10^{-05}	1.26×10^{-04}	2.93×10^{-06}	4.14×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
17	7.11×10^{-05}	1.22×10^{-04}	2.83×10^{-06}	4.00×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
18	6.92×10^{-05}	1.18×10^{-04}	2.76×10^{-06}	3.90×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
19	7.00×10^{-05}	1.20×10^{-04}	2.79×10^{-06}	3.94×10^{-06}	2.58×10^{-05}	7.80×10^{-05}
20 to <25	6.71×10^{-05}	1.15×10^{-04}	2.67×10^{-06}	3.78×10^{-06}	3.96×10^{-05}	1.20×10^{-04}
25 to <30	6.42×10^{-05}	1.10×10^{-04}	2.56×10^{-06}	3.62×10^{-06}	4.30×10^{-05}	1.30×10^{-04}
30 to <35	6.30×10^{-05}	1.08×10^{-04}	2.51×10^{-06}	3.55×10^{-06}	4.73×10^{-05}	1.43×10^{-04}
35 to <45	6.21×10^{-05}	1.06×10^{-04}	2.47×10^{-06}	3.50×10^{-06}	4.73×10^{-05}	1.43×10^{-04}
45 to <55	6.16×10^{-05}	1.05×10^{-04}	2.45×10^{-06}	3.47×10^{-06}	4.95×10^{-05}	1.49×10^{-04}
55 to <65	5.70×10^{-05}	9.74×10^{-05}	2.27×10^{-06}	3.21×10^{-06}	5.16×10^{-05}	1.56×10^{-04}
65 to <70	2.68×10^{-05}	4.59×10^{-05}	1.07×10^{-06}	1.51×10^{-06}	2.37×10^{-05}	7.15×10^{-05}

Table S.4 – Mean concentration of arsenic in drinking water, proportions of samples with inorganic arsenic concentrations above the maximum contaminant level and proportions of censured data, in Brazil as a whole and by region, in the 2014–2018 period.

Region	N or n	iAs concentration ($ng\ ml^{-1}$) Mean ± SD	Above the MCL (%)	Censured data (%)
Brazil	2448	3.0 ± 2.8	6.1	56.9
Southeast	1665	3.0 ± 2.6	6.0	49.3
South	548	2.0 ± 3.3	6.6	74.8
Northeast	82	2.0 ± 3.0	2.4	30.5
Midwest	136	0.4 ± 1.2	8.8	91.9
North	17	2.0 ± 2.9	0.0	82.4

iAs: inorganic arsenic; MCL: maximum contaminant level.

Source: Brandt et al. (2019).

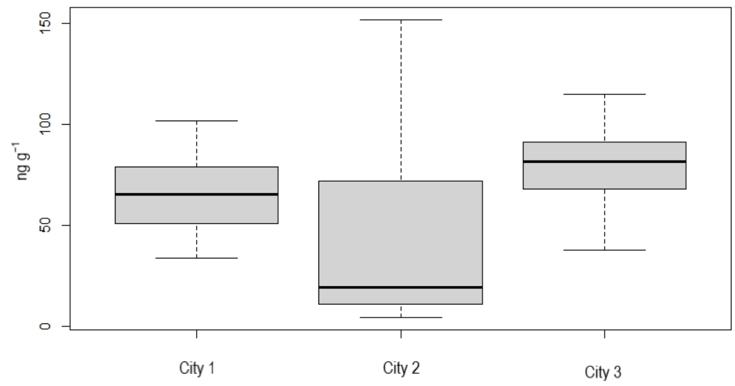

Fig. A1. Box plot of inorganic arsenic (iAs) concentrations in brown rice from farms by city.

5.2. MANUSCRITO II

Risk assessment from exposure to essential and toxic elements in infant cereal in Brazil

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Abstract

Infant cereals, one of the first solid foods introduced to infants, have been reported to represent risks to human health due the presence of toxic elements and the excess of essential elements. Rice cereal plays an important role in this scenario since it is immensely popular and usually has high levels of inorganic arsenic. The objective of this study was to assess the cancer and non-cancer risk of exposure to essential and toxic elements present in infant cereal in Brazil. We had access to data of 18 samples of infant cereals made from different row material and estimated the incremental lifetime cancer risk (ILCR) and hazard quotient (HQ). The elements included in this assessment was Ag, Al, As, B, Ba, Cd, Cr, Cu, Mn, Ni, Pb, Se, Sr, and Zn. Rice cereal was the kind of infant cereal with higher cancer risk and with more elements with HQ above 1. Inorganic arsenic was the element associated to higher cancer risk. All the infant cereals had an HQ above one for at least one element. Cd was the non-essential element more significative in this scenario, and Zn was the essential element more relevant. Avoiding infant cereals in early age can reduce the risk, and public polices can be positive to manage the risk in this complex scenario.

Keywords:
Rice
Arsenic
Metals
Early exposure
Food safety

1. Introduction

Infant cereals are one of the first solid food introduced to infants (Klerks et al., 2019). They can be classified as processed cereal-based foods, prepared primarily from one or more milled cereals and/or starchy root products. In general, they are simple cereals, and must be reconstituted with milk or other appropriate nutritious liquid (EC, 2006). There is a concern about the health risks related to the excess of essential and toxic elements present in some kinds of infant cereals (Paiva et al., 2019; Shibata et al., 2016).

Rice cereals stand out for usually having a high concentration of arsenic, which are associated to some cancer and non-cancer effects (U.S. FDA, 2016; U.S. EPA, 1995). Rice is recognized to store higher levels of arsenic, compared with other crops, what makes rice and rice products a significant source of arsenic to humans (U.S. FDA, 2016; Zhao *et al*. 2010). Rice cereals are widely used during weaning and to feed young children, and are popular due its availability, bland taste, nutritional value and relatively low allergic potential, especially for celiac population, since rice is gluten-free (Signes-Pastor et al., 2016; Shibata et al., 2016).

Not only can As pose risks to human health, but the presence of other non-essential elements in infant cereals made from different raw materials have been reported as a reason of concern as well (Hernandez et al., 2019; Hernández-Martínez and Navarro-Blasco, 2012). Some metals are considered systemic toxicants, associated to a variety of health damages, which depends on the metal, chemical species, and dose. Also, the characteristics of the exposed individuals are important, for instance age, gender, genetics, and nutritional status (Tchounwou et al., 2012). Arsenic, cadmium, chromium, and lead are known by their toxicity and carcinogenicity (ATSDR, 2020; Tchounwou et al., 2012; IARC, 2012; EFSA, 2009a). According to World Health Organization (WHO, 2010a), arsenic, cadmium, and lead feature in the list of 10 chemicals of major public health concern.

Other cereals used to process infant cereal are mainly wheat, corn, maize and oat flour, and are usually enriched with specific nutrients, thus they became a good option as complimentary food for infants and children (Klerks et al., 2019; Garcia-Casal et al., 2019; EC, 2006). Fortifying foods with essential elements is usually positive for public health and safe for the population (Garcia-Casal et al., 2019; EC, 2006). However, in some cases, it can increase the risk of adverse health effects, such as for copper, manganese and zinc (Garcia-Casal et al., 2019).

The age of exposure plays an important role in this complex scenario, especially regarding exposure to metals. Infants and children have high intestinal absorption capability, increasing the health risk (Jan et al., 2015). They have faster metabolic processes, and detoxification system in development. Children also present higher food consumption by body weight compared to adults, making exposure to hazard chemicals through diet an issue (Shibata et al., 2016).

In Brazil, infant cereals made from rice are widely consumed by infants and children, specially by infants who are weaning or celiac individuals. It has been reported that the consumption of infant cereal in Brazil might be an important route of exposure to some essential and non-essential elements (Pedron et al., 2016).

The objective of this study was to evaluate whether the levels of arsenic and other essential and toxic elements present in infant cereal are safe for consumption by infants and toddlers between the age of 4 and 24 months. We evaluated the cancer and non-cancer risks of consumption of rice-based cereal and non-rice-based cereal in Brazil.

2. Method

2.1. Average daily dose, carcinogenic risk, and hazard quotient

Average daily dose (ADD) was estimated assuming that exposure to elements present in infant cereal occurred between 4 and 24 months over the lifetime, as follows (U.S. EPA, 1989):

$$ADD_j = \frac{[C \times IRj \times EDj \times EFj]}{[BWj \times AT]} \qquad (1)$$

so that ADD_j is the average daily dose (mg/kg-day) for the age group j (4 to < 12 months, and 12 to < 24 months), C is the chemical concentration in infant cereal (mg/g), IR_j is the ingestion rate of infant cereal (g/day) for the age group *j*. ED_j is the exposure duration (8 and 12 months) and EF_j is the exposure frequency, both for the age group j*;* BW_j is the body weight for the age group *j*, and AT is the average time (ED_j x 365 days).

The cancer risk was estimated for each age group, aiming to identify if there are differences between them, and the incremental lifetime cancer risk (ILCR) for each infant cereal was obtained by summing the risk related to each age group, according to the equation (U.S. EPA, 2005):

$$ILCR = \sum_{j=1,n} (ADDj \times SF) \times \frac{ED_j}{LT}) \qquad (2)$$

where *SF* is the slope factor for the carcinogenic element, LT is the lifetime (70 years), and n is the number of age intervals (which are two).

The assessment for of non-cancer effects was made by the estimation of the fractional hazard quotient for each age group and each element. By summing that we obtained the Hazard Quotient (HQ), which is the ADDj divided by the RfD weighted by exposure duration j:

$$HQ = \sum_{j=1,n} (\frac{ADD_j}{RfD}) \times \frac{ED_j}{ED} \qquad (3)$$

The fractional HQ was weighted for the EDj related to the total exposure duration from 4 months to 24 months of age (1.67 years). The parameters adopted for the risk assessment are described in table 1:

Table 1: Parameters for the risk assessment

Parameter	**Unit**	**4 to < 12 months**	**12 to <24 months**	**Reference**
Body Weight (BWj)	kg	7.8	11.2	(IBGE,2010)
Exposure frequency (EFj)	days/year	365	365	(Shibata et al, 2016)
Exposure duration for each age group (EDj)	Years	0.67	1	(Shibata et al, 2016)
Ingestion rate (IRj)	g/day	31.2	94.08	(IBGE,2010; U.S. EPA, 2009)

2.2. Element's concentration in infant cereal

The concentration of essential and non-essential elements in infant cereal was obtained from a research made by Pedron et al. (2016), one of the few works about the concentrations of essential and non-essential elements in infant cereal in Brazil, which we had access. The authors obtained 18 Samples of 8 different brands of infant cereal: rice cereal (9), multi-cereal containing rice (5), and non-rice cereal (4). The samples were acquired in 2014-2015 period from different markets from four Brazilian states: São Paulo, Rio Grande do Sul, Distrito Federal, and Minas Gerais.

Total determination of essential and non-essential elements (Ag, Al, As, B, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Ni, Na, Pb, Se, Sr, and Zn) were carried out by an inductively coupled plasma mass spectrometer (ICP-MS). Arsenic speciation was conducted by using a high-performance liquid chromatograph (HPLC) coupled to the ICP-MS. The chemical speciation was carried out for one sample once the concentration of arsenic was below the detection limit for chemical (Pedron et al., 2016). Our risk assessment is focused on inorganic As (iAs), which is known to be carcinogenic. Thus, aiming to be conservative evaluating the worst scenario, we considered that iAs represented 100% of the total As (tAs). We also made an estimation of the risk considering iAs as a fraction of tAs, based on scientific data (U.S. FDA, 2016; Signes-Pastor et al., 2016; Pedron et al., 2016).

For this risk assessment only the elements with a described slope factor and reference dose were selected.

2.3. Selection of essential and non-essential elements for the risk assessment and its concentration in infant cereal

Among the 22 chemicals, five are assessed by the International Agency for Research on Cancer (IARC) (IARC, 2020): As, Cd, Al and Ni are group 1 (carcinogenic to humans), Pb is group 2A (probably carcinogenic to humans), and Se and Cr are group 3 (Not classifiable as to its carcinogenicity to humans). Only for two elements there are cancer slope factor available: iAs, which is 1.5 mg/kg-day (U.S. EPA, 1995), and Pb, 8.5x 10-3 mg/kg-day (OEHHA, 2020). For 15 elements there is an existing Reference Dose (RfD), described in table 2.

Table 2 – Reference doses (RfD) of the elements included for the risk assessment

	RfD (mg/kg-day)	Source
Ag	5.0×10^{-03}	IRIS
Al	1	ATSDR
As	3.0×10^{-04}	IRIS
B	2.0×10^{-01}	IRIS; ATSDR
Ba	2.0×10^{-01}	IRIS; ATSDR
Cd*	1.1×10^{-05}	OEEHA
Co	0.01	ATSDR
Cr	1.50	IRIS
Cu	0.01	ATSDR
Mn*	3.0×10^{-02}	OEEHA
Ni	1.1×10^{-02}	OEEHA
Pb**	3.5×10^{-03}	FAO
Se	5.0×10^{-03}	IRIS; ATSDR
Sr	6.0×10^{-01}	IRIS
Zn	3.0×10^{-01}	IRIS; ATSDR

*Child specific Rfd; ** RfD calculated according to the former FAO's provisional tolerable weekly intake (PTWI), which was withdrawn (Joint FAO/WHO, 2011).

3. Results and discussion

Table 3 shows the concentrations values of essential and non-essential elements in infant cereal, according to the main row material of the infant cereal obtained from Pedron et al., (2016), and table 4 presents the Maximum Contaminant Level (MCL) proposed by different agencies:

Table 3 – Essential and non-essential elements concentration in infant cereal (ng g^{-1}) (Pedron et al., 2016)

Infant cereal	Essential elements										Non-essential elements				
	Ag	**B**	**Ba**	**Co**	**Cr**	**Cu**	**Mn**	**Se**	**Sr**	**Zn**	**As**	**Al**	**Ni**	**Cd**	**Pb**
Corn cereal (A) *	0.00	0.00	307.95	6.45	109.35	1212.91	2481.93	62.01	6191.67	76980.20	4.75	2258.88	77.20	0.77	8.59
Oatmeal (B) *	24.67	135.03	3228.01	29.48	90.08	2663.27	25916.32	6.83	7350.02	92817.65	12.54	1751.27	498.52	1.58	26.66
Oatmeal (C) *	0.00	0.00	2314.38	11.69	82.52	3396.00	27957.60	53.31	6856.69	87975.73	6.29	3516.70	417.23	1.85	16.63
Multi-grain cereal(D) *	0.00	0.00	1268.78	11.62	118.01	1731.44	8076.69	37.05	992.36	132895.81	12.86	2797.43	82.26	9.52	31.30
Rice and oat cereal (E)	10.47	820.81	580.32	14.47	339.80	2939.32	16123.31	754.05	7.99	40778.36	26.32	8799.73	416.49	3.43	60.13
Rice and oat cereal (F)	11.79	142.63	1101.32	19.86	49.53	1583.76	10347.66	31.04	47843.81	66817.50	122.67	3870.41	182.15	12.97	25.52
Rice cereal and fruits(G)	32.16	1908.55	1211.96	61.22	209.50	4225.63	13222.21	45.06	3246.27	15987.85	90.98	4723.68	358.29	14.27	28.05
Rice cereal and maize starch (H)	0.00	0.00	414.44	14.46	383.63	3113.82	13189.60	48.59	16535.69	67200.60	18.92	4670.31	484.46	4.33	22.57
Rice cereal and maize starch (I)	0.00	0.00	3.56	5.30	138.97	202.41	1022.39	47.55	85.15	108784.53	17.05	1264.50	80.63	3.06	20.26
Rice cereal (J)	0.00	0.00	303.14	11.93	93.87	1729.32	7024.22	26.90	4649.73	69740.57	113.45	0.00	173.25	2.07	49.97
Rice cereal (K)	21.64	0.00	336.43	23.34	71.43	2053.55	10304.56	1001.25	32.41	121475.24	113.65	552.00	220.74	17.14	24.71
Rice cereal (L)	0.00	0.00	214.47	27.82	60.39	2198.62	11485.59	32.87	775.21	126856.65	125.70	81.36	172.05	19.13	32.04
Rice cereal (M)	32.90	310.60	567.04	17.65	266.53	1888.35	14092.72	28.10	1128.08	124412.43	146.27	0.00	183.32	22.15	20.52
Rice cereal (N)	27.39	1062.21	148.01	24.54	69.97	1953.83	9080.14	47.81	123.22	114733.40	102.36	2409.44	112.79	13.87	22.67
Rice cereal (O)	64.63	0.00	422.87	74.73	180.24	2928.29	15125.22	53.46	177.21	106956.31	168.08	865.44	264.91	18.71	15.58
Rice cereal (P)	17.01	1572.62	1192.17	54.56	211.67	4299.29	14414.66	42.69	3959.14	57728.65	86.71	4961.73	432.94	10.86	16.37
Rice cereal (Q)	48.57	0.00	441.57	33.17	38.36	2866.51	9949.67	13.54	6923.74	53445.06	130.85	3549.55	214.89	12.52	33.19
Rice cereal (R)	1.09	0.00	56.21	14.80	211.16	335.09	1616.48	826.97	5.21	130184.69	15.27	0.00	78.03	2.29	31.24

* Non-rice-based cereal.

Table 4 – Maximum Contaminant Level (MCL) of metals in infant cereal (ng g-1) according to different agencies

Country	iAs	Total Cd	Total Pb	Reference
Brazil	150	50	50	(Ministry of Health, 2017)
USA	100	-	-	(U.S.FDA, 2016)
European Union	100*	40	50	(EC, 2015a; EC, 2015b; EC, 2014)

*MCL for rice destined for preparation of infant and children food.

Among the 18 samples of infant cereal, if we consider iAs represents 100% of tAs, only one sample presented a concentration above the Brazilian MCL, and 8 samples (44%) are not in agreement with the MCL proposed by the United States Food and Drug Administration (FDA), and the Commission Regulation from European Union (EC). However, in our study, the data we had access is almost all about total As in infant cereal, because the concentrations were so low that speciation showed to be impractical. Thus, it is likely that the concentrations of iAs of all samples are below the three MCL. The authors made the speciation of iAs in one sample of rice cereal from Brazil, the one with the highest concentration, and found that iAs content corresponded to about 40% of tAs (Pedron et al., 2016). Signes-Pastor et al. (2016) found that iAs percentage in samples of rice cereal ranged from approximately 14% to 90%. The FDA (2016) reported that on average, the concentration of iAs in 69 samples of infant cereal was 120 ng g^{-1}, representing around 60% of the total. If we consider iAs corresponding to 90% of total As, there would be 7 samples with concentration above the EC and FDA MCL. In case of iAs represent 80%, 70%, 60% e 50% of total As, we would have 4, 2, 1 and zero samples with the concentration above the mentioned MCLs, respectively.

According to data by Pedron et al. (2016), showed in table 4, rice-based cereal has higher levels of tAs (111.37 ± 43.23 ng g^{-1}), compared to multi-grains cereal with rice (48.13 ± 46.76 ng g^{-1}), and no-rice-based cereal (7.86 ± 4.12 ng g^{-1}). This agrees with an independent study conducted in the United States of America (USA), with an average concentration of iAs of 85 ng g^{-1} in rice-based cereal, in contrast to 23 ng g^{-1} in multi-grains with rice cereal, and 17 ng g^{-1} in multi-grain with no rice cereal, and 13 ng g^{-1} in oatmeal (HBF, 2017). The FDA (2016) reported a concentration of 105 ng g^{-1} of iAs in dry white-rice cereal, and 120 ng g^{-1} in dry brown-rice cereal. In Argentina, Londonio et al. (2019) found a concentration of 80.4 ng g^{-1} of tAs in one sample of rice cereal, however no statistical conclusions could be drawn.

Regarding the other elements found in infant cereal, two samples (rice and oat, and rice cereal) have concentration of Pb above the Brazilian (Ministry of Health, 2017), and EC MCL (EC, 2015a). In Spain, high levels of Pb in infant rice cereal (116 ± 37 ng g-1) were reported. The authors highlighted the necessity of effort to identify the source of Pb and to reduce the levels of this contaminant in rice-based infant foods (Carbonell-Barrachina et al., 2012a). Recently, FAO considered the proposed provisional tolerable weekly intake (PTWI) for Pb could no longer be considered health protective, thus it was withdrawn, which means that no dose of Pb is considered safe. All samples have a concentration of Cd under the MCL.

3.1. Cancer risk of exposure to non-essential elements in infant cereal

Table S1 (in the supplemental material) presents the incremental cancer risks by age group and the ILCR for iAs, Pb and both combined. Figure 1 presents the box plot of the total ILCR.

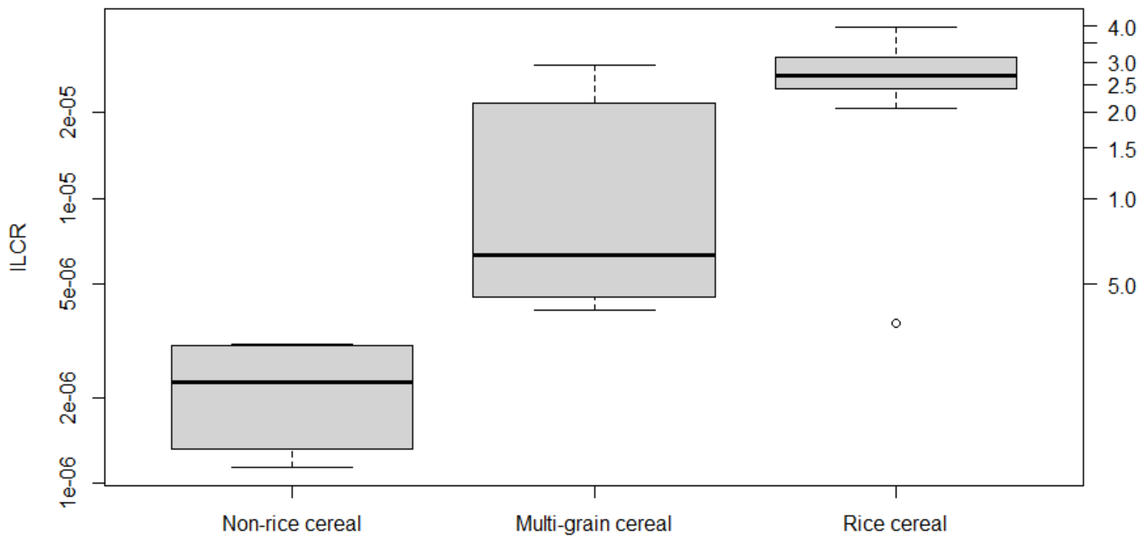

Figure 1: Box plot of the ILCR from exposure to iAs and Pb in infant cereal according to its composition, in logarithm scale.

The ILCR, for exposure to iAs and Pb, for all samples of infant cereal ranges from 1.14 x 10^{-6} (corn cereal) to 3.99 x10^{-5} (rice cereal). The age group with higher cancer risk found is from 12 to 24 months. The ADD for this age group is about double compared to the 4 to 12 months (table S2). The rice ingestion from 12 to 24 months of age is 8 g/day per kg of body weight, more than double compared to 4 to 12 months, which is 4 g/day per kg of body weight. The exposure duration must be considered too, which is longer than for 12 to 24 months. Interrupting the exposure from 4 to 12 months by delaying the weaning until the first year of life could reduce the cancer risk in 24%.

Rice-based cereals presents the highest ILCR (ranging from 3.7 x 10^{-6} to 4,0 x 10^{-5}), followed by multi-grain cereal, which contain rice (from 4.1 x 10^{-6} to 2.9 x 10^{-5}) and non-rice cereal (from 1.1 x 10^{-6} to 3.1 x 10^{-6}). The higher risks can be attributed to the high concentration of iAs, typical of rice and rice products. Rice is recognized to store higher levels of arsenic, compared to other crops (Joint FAO/WHO, 2017). On average, the ILCR for rice cereal (2.6 x 10^{-5}) is two times higher than for multi-grain cereal (1.3 x 10^{-5}), and about 12 times higher than the ILCR for non-rice cereal (2.2 x 10^{-6}). Signes-Pastor et al. (2016) found a good correlation between iAs and rice content in infant cereal, confirming that most of the iAs is coming from rice. We found some variability in the risk results, even among the samples of rice cereal, which can be related to the amount of rice or other cereal, the rice origin and manufacturing process (Signes-Pastor et al., 2016).

In fact, iAs represented the largest portion of ILCR in all samples**,** including non-rice cereals, ranging from 98.5 to 99.9 % of the total ILCR. iAs has a high cancer slope factor (1.5 mg/kg-day-1) which is more than 176 times higher than the slope factor of Pb ($8.5x10^{-3}$ mg/kg-day-1).

Infant cereal can represent the main source of iAs for infants and children, as described by Shibata et al. (2016). In their study, the ILCR from diet exposure during infancy was 10^{-5}, and rice cereal represented 55% of the dose of iAs for infants and children between four and 24 months, followed by other infant solid food (19%), drinking water (18%) and infant formula (9%).

The concentration of arsenic in foodstuff is influenced by the food type, growing conditions, and food-processing techniques. Arsenic is a ubiquitous metalloid, and it exists as organic or inorganic. Exposure to iAs is associated to some cancer and non-cancer effects. The International Agency for Research on Cancer (IARC) classified iAs as a group I carcinogen, with the potential to cause skin, lung, bladder, and kidney cancers (IARC, 2012). The oral exposure to iAs is also associated to skin lesions, diabetes and impacts in the cardiovascular and immune systems (ATSDR, 2007).

The organic form of arsenic is an arsenic compound that contains carbon, which includes monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) (Joint FAO/WHO, 2017). There is scarce information available about the health effects in humans related to organic arsenic compounds, most of the studies was conducted with animals, what increases the uncertainty since there is evidence that animals are less sensitive to arsenic than humans (ATSDR, 2007). Organic arsenic is considered by the IARC not classifiable as to their carcinogenicity to humans (Group 3). The FDA, in its Risk assessment of exposure to arsenic in rice and rice products, collected evidence in literature about organic arsenic, indicating that the exposure to some organic arsenic compounds could be related to effects on the urinary bladder, kidneys, thyroid, fetal development and the gastrointestinal tract (U.S. FDA, 2016).

In rice paddies, the land is usually flooded and under anerobic conditions, arsenate (As V), an inorganic form of arsenic, is reduced to arsenite (As III), which is more mobile and bioavailable for plants. Other sources of iAs to rice is the water used for irrigation, and the use of pesticides and fertilizers (Joint FAO/WHO, 2017; Zhao et al., 2010).

In our study we focused only in iAs, which has more available information, thus the actual risk can be higher than we estimate. Also, we only have data about total arsenic in infant cereal, not iAs which would be more appropriate since the available slope factor was developed for iAs. According to a few studies the proportion of iAs in infant cereal ranges from 14 to 90% (U.S. FDA, 2016; Signes-Pastor et al., 2016; Pedron et al., 2016). Considering the median of that percentage, we estimated the cancer risk for iAs representing 52% of total As, as described in table S3.

The new estimation of risk related to iAs in infant cereal, representing 52% of the previews risk, represent a range risk of 5.9×10^{-7} to 2.1×10^{-5}. It indicates how the concentration of iAs can impact the risk, and the importance of the speciation and reduction of iAs in infant cereal. In this new estimation, the risk related to iAs is between 97.2 – 99.9% of the total risk, keeping the lead in a less relevant position.

The ILCR we found, even considering iAs to be a fraction of tAs, can be thought high. There is no guideline of acceptable risk related to carcinogenic contaminants in food, but if we consider the acceptable risk suggested by the WHO (WHO, 2017a) for carcinogenic compounds drinking water (10^{-5}), as did some authors such as Shibata et al., (2016), our ILCR would be 3.99 (more conservative scenario) or 2.1 (iAs representing 52% of tAs) times higher than that guideline. Additionally, this risk assessment is considering exposure only for a life stage and only for one kind of food, so the actual risk might be higher. Other kinds of food have been reported as important sources of exposure to As, such as fish, seafood, and food products or supplements based on algae (EFSA, 2009b). In some locations, the presence of As in drinking water is a public health issue, primarily due its natural occurrence in groundwater, which is significative for China, Taiwan, Bangladesh, and West Bengal (India). More punctual occurrence has been reported Argentina, Australia, Chile, Mexico, the USA, and Vietnam. Anthropogenic sources have contaminated some water sources in Japan, Mexico, Thailand, Brazil, Australia, and the USA (IARC, 2004).

The ILCR corresponding to Pb in infant cereal ranged from 1.15×10^{-8} (corn cereal) to 8.08×10^{-8} (rice and oat cereal). On average, the ILCR is higher for multi-grain cereal (4.2×10^{-8}), followed by rice cereal (3.7×10^{-8}), and non-rice cereal (2.8×10^{-8}). The ILRC corresponding to Pb is considered low, compared with the WHO guideline for drinking water (WHO, 2017), and significantly lower than the risk related to iAs.

Exposure to Pb occurs more commonly by ingestion of contaminated food and drinking water, and through ingestion of contaminated soil or dust, and lead-based paint (ATSDR, 2020). Lead is found in all categories of food, and the sources are mainly soil remaining in or on the food, atmospheric deposition, contact with lead-containing processing equipment and packaging (JECFA, 2011). Children are more vulnerable to Pb, and the most common source of exposure are lead-based paint (ATSDR, 2020). In addition to being carcinogenic, early exposure to lead is associated with damages to the neurological system, such as attention deficit, difficulty concentrating and learning, decreased motor skills, and increased aggressive behavior (Zhang et al., 2013; WHO, 2010b; Olympio et al., 2010; 2009).

Neto et al. (2019) conducted a systematic review and meta-analysis with the main goal of estimate the Pb content in food consumed or produced in Brazil. They found that infant food, which includes infant cereal, was the food category with the highest mean concentration of Pb (0.48 mg/kg). They identified relevant uncertainty about the results of infant food, mainly attributed to the lack of data. Leroux et al. (2018) found that, compared with other countries, Brazilian preschool children’s diet did not contain high arsenic and lead levels. Although, given the overall exposure, they considered that diet may contribute significatively to health risks. The authors argue that there is no safe level for lead exposure. In Sao Paulo, Brazil, Olympio et al

(2018) found in a cross-sectional study that the blood lead levels in children from 50 day care centers were almost three times higher than those in U.S children. Their finds suggest hot spots for lead exposure, also higher vehicles flow and red lead in household gates were identified as important risk factors for lead exposure. The authors highlighted the importance of choosing locations with lower traffic flow for the day care centers construction-planning phase, indicating that this initiative may minimize the exposure of preschool children.

Aluminum, cadmium, and nickel are elements with evidence of carcinogenicity, but they were not included in this risk assessment due the lack of slope factor. Thus, the ILCR from infant cereal intake is probably higher than the described in this research.

Exposure to Al compounds can affect the reproductive and nervous system, even at low doses. Non-occupational exposure to Al is mostly through ingestion of water and principally food, and it is naturally present in most foodstuffs consumed. Plants and cereals can absorb Al from soil and water, and the sources can be natural or artificial. Furthermore, another source of Al to food are aluminum-containing additives (Joint FAO/WHO, 2018).

Food is the main route of exposure to Cd, excluding some occupational activities and smoking (Jean et al., 2018). Based on the high consumption, cereals and cereals products, vegetables, nuts and pulses, starchy roots or potatoes, and meat and meat products are the food groups that contribute to a major part of the dietary Cd exposure. For infants and young children, processed cereal based foods are a significant source of exposure to Cd (EC, 2014). The source of Cd to food are contaminated soil and water, from natural sources and from anthropogenic activities (Joint FAO/WHO, 2011).

Human exposure to Ni occurs mainly through ingestion of food, but also water, inhalation of ambient air, cigarette smoke, occupational activities and dermal contact with coins and jewelry containing nickel (Ferreira et al, 2019; ATSDR, 2005a). Some foods have a higher concentration of nickel, such as chocolate, soybeans, nuts, and oatmeal (ATSDR, 2005a). The source of Ni to food and drinking water can be both natural and anthropogenic (EC, 2016).

3.2. Non-cancer risk of exposure to essential and non-essential elements in infant cereal

Table S4 shows the results of the non-cancer risk assessment for each element and each cereal. The elements that are related to an HQ above 1 are presented in figure 2.

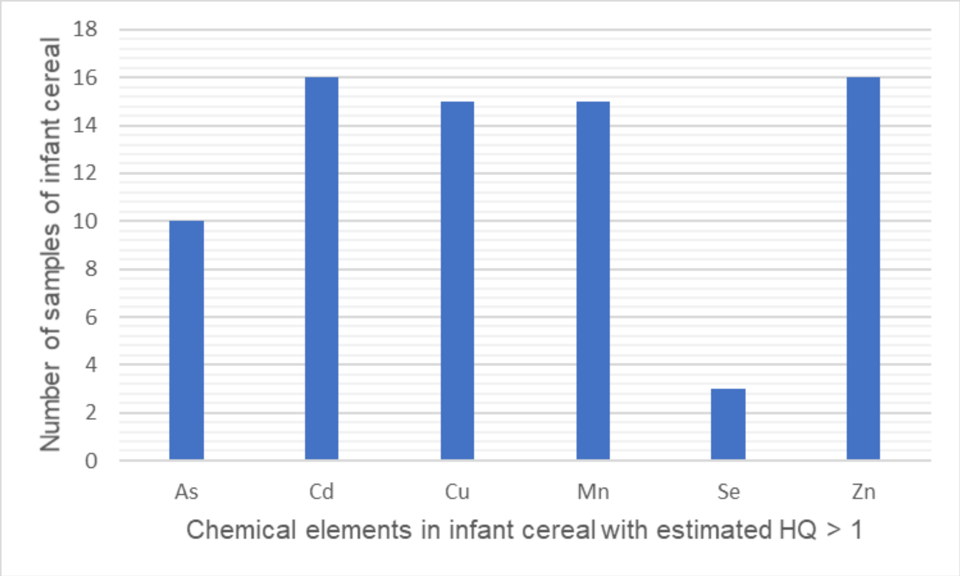

Figure 2 – Elements present in infant cereal and the number of samples in which the HQ was estimated to be above 1

All infant cereals have HQ exceeding 1 for at least one element (table S4), which means that the daily dose is higher than the reference dose, and health effects are likely. Six chemicals are responsible for HQ above 1 (As, Cd, Cu, Mn, Se and Zn) as shown in figure 2. Cd, Cu, Mn and Zn are the elements that represented more HQ above 1 (between 15 and 16 samples), and Se was the one with less (3 samples).

Proportionally, rice cereal has more elements with HQ above 1 (81.5%), followed by Multi-grain cereal (52.8%), and non-rice cereal (50.0%). A study with more samples of infant cereal would provide a more sophisticated statistical analysis.

Some of the chemicals with HQ above 1 are essential elements (Cu, Mn, Se and Zn), needed by the human body only in small amounts, and toxic effects are expected if the dose of exposure exceeds certain levels (Zoroddu et al., 2019).

Garcia-Casal et al. (2019) reported in their review that might be a risk of excessive intake of certain essential elements due ingestion of fortified food, especially in countries where there are simultaneous micronutrient-delivery interventions. They also found that stablishing a recommendation on the maximum amount of certain essential elements to be allowed in food products is a challenge, and risk management could be an important tool to support the decision making. Another aspect to consider is that the levels of certain nutrients in infant cereal can be significantly higher than in breast milk, which can be very concerning since the high prevalence of infants that are introduced to this kind of food before 6 months of live (Sipahi et al., 2015).

Cu is an essential element, and its main source of exposure is diet, but foods have low amounts of cooper usually not representing risks to human health. Exposure to excessive levels of copper can result in anemia, developmental toxicity, and damages to the liver, kidney, and the immunological system (ATSDR, 2004). Carbonell-Barrachina et al. (2012) evaluated different kinds of infant food, and infant cereals were among the kind of food with higher levels of Cu.

Food is the primary source of Mn exposure for the general population (ATSDR, 2002). High amounts of Mn are present in whole grains (wheat germ, oats, and bran), rice, and nuts (hazelnuts, almonds, and pecans), thus Mn deficiency is remarkably rare (Aschner and Erikson, 2017). Even so, infant formulas are usually fortified with Mn (Hardy, 2009). Ljung et al. (2011) reported that the intake per portion of infant cereal represented a higher intake of Mn (26–2800 times), compared with breast milk. Hight oral doses of Mn are related to neurological effects (Aschner and Erikson, 2017). Sipahi et al. (2015) evaluated different kinds of infant food and found cereal-based food to have higher levels of Mn, and in some cases, the consumption would represent an inadequate intake of this element.

The exposure to Se occurs mainly through diet. Food grown in soils rich in Se tend to absorb more of this essential element. Grasses and cereal plants can store high amounts of Se (Mehdi et al., 2013). Some locations of China are known to have soils rich in Se, and selenosis is a public health problem in a way that agriculture in these areas is discouraged (FAO/WHO, 2001). Selenosis is a disease resulted from long-term oral exposure to high doses of Se, and is characterized mainly by hair loss, and brittle nails (Mehdi et al., 2013). On the other hand, Se is associated to reduce the toxicity of As and Cd, both carcinogenic elements and with toxicity potential (Zwolak, 2020). Carbonell-Barrachina et al. (2012a) assessed the essential elements content of different infant cereals and found that the concentrations of Se were independent of the cereal type. In our study the Se content represented risk only in two samples of rice cereal, and one sample of rice and oat cereal.

The exposure to Zn, for the general population, occurs by the ingestion of food, drinking water, polluted air, and tobacco product. Exposure to high oral doses can result in symptoms and signs of gastrointestinal irritation, and a long-term oral exposure to Zn can cause a decrease in copper absorption. Copper deficiency in turn is associated with decreased number of erythrocytes and decreased hematocrit levels (ATSDR, 2005b). On the other hand, Zinc deficiency is a malnutrition worldwide, especially in children and women whose diets are cereal based. Cereals are rich in fiber and phytates, which reduce the zinc absorption from the intestine. Fortifying staple foods with zinc is used as a strategy to address this public health issue, and infant cereal usually go through this process. The health benefits of this actions are uncertain, and no adverse effect have been reported. The bioavailability and absorption of zinc play an important role regarding health effects and health benefits (Shah et al., 2016). Garcia-Casal et al. (2019) argue that in the case of some elements, such as zinc, the consequences of a high intake appear to be minimal, and the consequences of deficiency are severe in low-income settings, including increased morbidity, mortality, and stunting. Thus, the decision maker must take this complexity into account.

On the other hand, iAs and Cd are non-essential trace elements, and any exposure to them is undesirable and may cause adverse health effects in infants even at low levels. Toxic minerals or trace elements may be present in infant food primarily because of their natural occurrence in the raw materials (Carbonell-Barrachina et al., 2012a).

Ljung et al. (2011) evaluated different kinds of infant food and found that the intake of arsenic present in these foods to be much higher (1 — 95 times) than by infants of 4 months of age having breast milk. Carbonell-Barrachina et al. (2012a) call the attention for the diets of celiac people, which is richer in iAs than the population in general. They identified that gluten-free infant food usually has rice in its composition, increasing the levels of iAs. The non-cancer effects related to oral exposure to iAs are skin lesions, diabetes and impacts in the cardiovascular and immune systems (ATSDR, 2007). In our study, the lack of data about the iAs in the samples is a limitation, since the RfD is attributed to iAs, not total As. If we consider iAs representing 52% of total As, following the same assumptions made for the cancer risk estimation in section 3.2, we will have a decrease in the HQ results, as described in table S5.

Even with the HQ values representing only 52% of the preview's HQ estimations, the number of samples with HQ > 1 remains the same, thus 10 samples of infant cereal (rice and oat cereal, rice cereal and fruits, and just rice cereal) might represent risks to human health.

Cadmium represented the non-essential element with relevant risk for more cereal samples. The dietary exposure to Cd can result damages to the kidney and can cause bone demineralization. Cd can be retained in the kidney and liver, with a biological half-life varying from 10 to 30 years (EFSA, 2009a). In a study assessing different kinds of infant food, the authors found that baby rice and infant rice had the highest content of Cd (Carbonell-Barrachina et al., 2012a). Cereal-based food can have higher levels of Cd, compared to milk-based food, as reported by Sipahi et al. (2015). In an estimation of the intake of Cd from infant food, Ljung et al. (2011) found it be higher (3-270 times) than from breast milk for infants of 4 months of age. In France, Jean et al. (2018) found that a high proportion of children exceed the Cd tolerable weekly intake of 2.5 μg/kg bw^{-1} proposed by the European Food Safety Authority (EFSA). Infant cereals were among the main contributors to that. The authors state that the exposure to Cd should be reduced to prevent health issues. In Sao Paulo, Brazil, Olympio et al (2018) found the blood cadmium levels children (age) to be almost twelve times higher (95th percentile) than in children from the United States of America, a country with strong public policies related to chemical exposure. In their cross-sectional study, they included 2,463 children from 50 day care centers. The authors identified hot spots of exposure to Cd and concluded that it is necessary to give priority to identify and control it in Sao Paulo, where preschool children can be exposed to metals.Rice-based cereal represent a higher concern about the non-cancer risk, with on average 4.7 elements resulting in HQ>1, in contrast of 3.5 elements in non-rice-based cereal.

Excluding the infant cereal intake from 4 to 12 months of age could reduce the number of elements with HQ above one. This applies to Cu (5 samples) and Se (2 samples). Replacing breastfeeding with inappropriate supplementary feeding, especially in the first six months of life, can be characterized as a risk factor for morbidities and mortality. Long-term impacts are poor school performance, lower productivity, and reduced intellectual and social development (WHO, 2003). Breastfeeding can reduce the risk of type 2 diabetes and overweight/obesity (Horta et al, 2015). Exclusive breastfeeding in early life has a protective effect on gastrointestinal and allergic diseases (Kramer, 2004).

HQ is below 1 for Ag, B, Ba, Co, Cr, Ni, Sr, Al and Pb. The HQ for Pb was calculated with an estimation of RfD, based on the previews PTWI proposed by Joint FAO/WHO. Recently the PTWI was withdrawn, because it was concluded that the PTWI could no longer be considered health protective (JECFA, 2011). Thus, besides our results, there is no level of Pb exposure that are considerate safe at this moment. Carbonell-Barrachina et al. (2012a) reported that among different types of infant food, infant cereal and rice cereal was recognized to have the highest concentrations of Pb.

3.3. Understanding the risk scenario in Brazil, and adopted practices to reduce the risk in different countries

Important measures to mitigate the risk are mainly related to reduce the chemicals concentration in infant cereal or to reduce the ingestion of cereals. In the USA, the FDA proposed in their risk assessment three hypothetical scenarios where mitigation actions were taken: stablishing iAs limits for infant rice cereals, changing the frequency of the consumption of infant rice cereals, and combining both actions, which presented the most significative reduction of iAs intake (from 153 ng/kg bw/day to 32 ng/kg bw/day or less) (U.S. FDA, 2016). In another report, the FDA (2020) stated that it is possible to reduce the exposure to iAs from rice cereal through industry’s use of current good manufacturing practices, highlighting the selection of rice with low iAs concentration. They proposed an action level of 100 µg/kg (100 ng g^{-1}), which was based on previous experiences, thus they considered it achievable and protective to public health.

Carey et al. (2018) identified that to accomplish a standard of 100 ng g^{-1} of iAs in infant food proposed by the European Commission in 2016, the manufacturers were diluting rice with other gluten free cereals. Hernández-Martínez and Navarro-Blasco (2012) identified that some cereal producers in Spain have accomplished considerable reductions of non-essential element levels, likely through selection of raw materials and prevention of contamination during industrial manufacturing. The data of rice cereal samples we are using in this study (Pedron et al, 2016), have a mean concentration of total arsenic of 111.4 ± 43.2 ng g^{-1} (confidence interval of 78.14–144.6), thus slightly higher than the 100 ng g^{-1} proposed by the FDA for iAs. It is possible that an arsenic speciation revels a concentration of iAs below the proposed standard. There is a significative variability in the As concentration, and the small number of samples is not representative of the rice infant cereals consumed in Brazil.

Reducing the intake of rice cereal could be achieved by balancing the kind of infant cereal offered to infants and children. As shown in table 4, the type of cereal can contain different concentrations of a variety of elements and can represent distinct levels of risk (table S1). The type of cereals given to infants varies according to the culture of the country. Rice, oats, wheat, and maize cereal appear to be the most popular (Klerks et al., 2019). Infants and children usually have a less varied diet than adults, increasing the concern about exposure to non-essential elements and health risks. Infants and children also are a more vulnerable population because they consume more food relative to their body weight than do adults (U.S. FDA, 2020).

In Brazil we have a few studies investigating the kind of infant cereal consumed by infants and children. Albuquerque et al. (2018) reported that among the 63 infants (0 to 6 months of age), in a peripheric area of the Northeast of Brazil, the infants usually had more than one kind of infant cereal, and rice cereal was the most prevalent (> 76%), followed by maize starch (29%), multi-cereal composed by wheat, barley and oats (10%), and oatmeal (3%). Approximately 90% of the infants had between 2 and 8 portions of infant cereal, infant formula, or whole milk per day. Still in Northeast of Brazil, Sombra et al. (2017) found rice cereal to be the most prevalent choice of infant cereal (27%), followed by corn cereal (20%), wheat cereal (10%), maize starch (7%), oatmeal (5%), and multi-cereals (3%). The study was conducted with 60 children from 4 to 36 months.

Other mitigation actions to reduce the risk is adopting good agricultural practices, and monitoring soil and water contamination. The concentration of iAs in rice can vary significantly depending on agricultural practices and environmental conditions. In Brazil, Kato et al. (2019) found a difference by two orders of magnitude in rice samples grown under different water conditions, locations, and cultivars of rice. In the South of Brazil, the main rice producer region of the country, Monteiro et al. (2020) found significant differences on the accumulation of essential and non-essential elements in rice. They attributed it mainly to environmental conditions, and second was the rice variety. Segura et al. (2020) argue about the importance of crop-tracking, identifying rice with low concentration of iAs and use it for food production for vulnerable people, such as infants, children, and celiac people. In an exploratory study in Brazil, Lange et al. (2019) conducted with success rice traceability by cities, producers, and rice varieties.

Some added ingredients, such as cocoa, honey and fruits, can also be a source of some kinds of metals, like cadmium and lead, to infant cereal (Hernández-Martínez and Navarro-Blasco, 2012).

Regarding the excess of essential elements in infant rice, Garcia-Casal et al. (2019) declare that an important issue is the lack of data about intakes and actual deficiencies in the population. They agree that adding essential elements in infant food can be an important measure for public health, but they claim that in some situations it is possible that people are receiving more than is necessary. They recognize the challenge of this situation and indicate the necessity of having a more accurate surveillance, monitoring, and evaluation systems. The authors also suggest the necessity of a risk evaluation in a timely manner and a strong monitoring system.

Reducing the concentration of elements in infant cereal or having a variety of infant cereal probably would not solve the problem if the infants have early food introduction. In this study we considered infants starting to consume infant cereal at 4 months of age, since many studies have reported early breast feed interruption, and found that infant formula and infant cereal is usually the food chosen to replace breast milk (Albuquerque et al., 2018; Sombra et al., 2017).

In a study conducted with 63 infants, from 0 to 6 months of age, in a peripheric area of the Northeast of Brazil, Albuquerque et al. (2018) verified that 43% of the infants had an interruption on exclusive breast feeding before 1 month of age, and the rest of them with 4 months of live. Among these infants, 58.7% of them had infant cereal replacing breast milk, and the most prevalent period was from 0 to 4 months of age.

Sombra et al. (2017) found in a transversal study with 60 children (4 to 36 months) of low or middle income, from state of Ceará (Northeast Region of Brazil) that 10% of them were introduced to some complementary food before 4 months of age. The main reason was the necessity of the mothers to return to work. They identified a relevant prevalence of infant cereal given to children.

Following the WHO guidelines of exclusive breastfeeding until 6 months of age and continued breastfeeding with complementary foods for up to 24 months of age or older can be a challenge in Brazil, such as in many countries, and one important reason is the access to maternity leave (WHO, 2017b). This is a global issue, since less de 40% of infants have exclusive breastfeeding up to 6 months of life (WHO, 2015). In Brazil, the maternity leave of 120 days is guaranteed for women who are inserted in the formal labor market (Brasil, 2016). With informal labor and other formal arrangements of work raising, there is an increase in workers who do not have labor rights, including maternity leave (Brasil, 2009).

Monteiro et al. (2017) conducted a cross-sectional study with data from a national survey and found evidence that the lack of maternity leave can increase the chance of exclusive breastfeeding interruption by 23% for infants under 4 months of age in Brazil. In another cross-sectional study in Brazil (Rio de Janeiro), the authors found the prevalence of exclusive breastfeeding to be 50.1% in infants with less than 6 months of age, associated with maternity leave (Rimes et al., 2019).

There are determinants for breastfeeding at structural, community and workplace, and individual levels. The health system and the community have an important role on exclusive breast-feeding up to 6 months. A mother who has access to counselling and support at health facilities, with a supportive and enabling environment has more chances of exclusive and continued breastfeeding (WHO, 2018a). The lack of social protection, health care systems, breastfeeding counseling, prepared health care providers, and information are reported as important reasons for mothers to interrupt breastfeeding early. In addition, breast-milk substitutes advertisements were very relevant (Pérez-Escamilla, 2020).

Improper practices in the marketing of breast-milk substitutes and complimentary food, such as infant cereal, can lead to early weaning. Concerning about it, the WHO published the International Code of Marketing of Breast-milk Substitutes, which includes requirements about information and education related to infant feeding; labeling, ethical promotion and quality of breast-milk substitutes and related products. The code recommends that there should be no advertising or other form of promotion to the general public of breast-milk substitutes and related products (WHO, 1981). It has been reported that, contrary to what was proposed by the code, promotion of breast-milk substitutes infants and young children (6–36 months) is increasing. Also, some violations in health-care settings and advertisements are among as the most persistent (WHO, 2018b).

In Latin America, some reported reasons for early breastfeeding interruption were lack of support from family, previous experiences, psychological aspects, maternal work and breast problems related to breastfeeding. The lack of time showed to be an important reason for early weaning. Also, some mothers have the wrong concept that breastmilk is not enough to feed their infants (Kamya et al, 2019; Neri et al, 2019; Capucho et al, 2017).

Breastfeeding contributes significantly to public health cost savings. Preventing diseases can result in fewer hospital admissions and consultations. A study conducted in the United Kingdom, considering four infant acute diseases, over £17 million could be gained annually (UNICEF, 2012). Having the context of the economic impact of breastfeeding, Smith et al (2013) evaluated the time taken to exclusively breastfeed at 6 months compared with not exclusively breastfeeding. They found that mother who chose exclusive breastfeeding spent more hours in this activity, which is economically costly to women. They believe that it may contribute to early weaning, and argue that public policies are necessary, providing, for instance, additional help with housework or caring for children, enhanced leave, and workplace lactation breaks and suitable childcare.

Some governmental initiatives promote maintaining exclusive breastfeeding up to 6 months through educational programs and the creation of organized groups of mothers to exchange experiences for mutual support. There is evidence that these initiatives have been effective (Venancio et al., 2016; Rito et al., 2013). Other strategies adopted by the Brazilian government is the stimulation of public and private companies having a daycare at the workplace and a breastfeeding support room (Fernandes et al., 2017; Ministry of Health, 2015; Ministry of Health, 2010), and the right to two extra breaks to breastfeed (BRASIL, 1943). A national law created in 2008 guarantees that civil servants have 180 days of maternity leave and 20 days of paternity leave, which regularly is 5 days. The same conditions are guaranteed for employees of companies that adhere to the Program, stimulated by tax incentives (Brasil, 2008). Although, the adherence by the private sector is low, in 2016, only about 10% of the companies in Brazil committed to the Program (Brasil, 2008).

Thus, it is common that finished the maternity leave the infants start to spend the day at daycare centers, when usually the breast feeding is interrupted. In Sao Paulo, the food consumption guideline for the daycare centers of the municipality suggests that infants (0–3 months) have infant formula, and the introduction of vegetables, rice, meat, and fruits starts at 4 months of age (São Paulo, 2011).

In this study we conducted an analysis based on the assumption of a daily cereal intake. Actual doses for individuals vary according to their diet. The cereal intake can vary according to different countries, families, regarding dietary patterns at school and at home, or comparing rural and urban areas. The culture, politics, economy, demography, and social issues are factors that can influence the dietary pattern of an individual (Vieira et al., 2017; Lima et al., 2018; Barroso et al., 2014).

The results we found highlight the importance of avoiding infant cereal consumption in early ages, promoting exclusive breastfeeding until 6 months of age, which must be supported by public policies. The introduction of complimentary foods should be conducted with a balanced diet. Barroso (2014) found in a study performed in a metropolitan area of Rio de Janeiro, Brazil, that parental food intake is associated with children’s intake. Therefore, strategies to offer nutritional guidance to the parents can be positive to the health of infants and children.

4. Conclusions

According to our risk assessment, rice cereal was the kind of infant cereal in Brazil representing higher cancer risk and with more elements with HQ above 1. The higher cancer risk is attributed to the typical high concentrations of iAs in rice.

Inorganic arsenic was the element associated to higher cancer risk, even for non-rice cereal. For the non-cancer risk, cadmium was the non-essential element more significative, and zinc was the essential element more relevant. Even the cancer and non-cancer risk for lead is relatively low, the exposure to this element is always concerning, especially regarding to a vulnerable population.

Delaying the introduction of infant cereals until one year of age can reduce the risk. We emphasize the importance of breastfeeding, which in addition to the already known benefits, can be a safer food source in terms of avoiding non-essential elements and the excess of essential elements.

More studies are necessary to manage the risk, but the literature suggests a complex scenario involving maternity leave, culture, brands advertisements’ influence, and agricultural and industrials practices. Some studies have pointed a direction to address the risk, and public polices in some countries presented results to reduce the iAs concentration in infant cereal.

Our findings reflect the exposure scenario we adopted, which have some uncertainties. Having more data would allow us to conduct a probabilistic risk assessment and to reach a more statistical significative result.

The actual risk for infants is probably higher than we reported since we have not included some elements in the assessment due the lack of cancer slope factor and reference dose. A different result could be found if we include other kinds of food consumed by infants (such as infant formula) and drinking water, potential sources of iAs.

5. References

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Suplementary material

Table S1 – Estimated incremental cancer risks and incremental lifetime cancer risks (ILCR) associated with exposure to non-essential elements present in different kinds of infant cereal.

Infant cereal	Age group	iAs	Pb	Total
Corn cereal (A)	4 to < 12 months	2.72×10^{-07}	2.78×10^{-09}	2.74×10^{-07}
	12 to < 24 months	8.55×10^{-07}	8.76×10^{-09}	8.64×10^{-07}
	ILCR	$\mathbf{1.13 \times 10^{-06}}$	$\mathbf{1.15 \times 10^{-08}}$	$\mathbf{1.14 \times 10^{-06}}$
Oatmeal (B)	4 to < 12 months	7.16×10^{-07}	8.63×10^{-09}	7.25×10^{-07}
	12 to < 24 months	2.26×10^{-06}	2.72×10^{-08}	2.28×10^{-06}
	ILCR	$\mathbf{2.97 \times 10^{-06}}$	$\mathbf{3.58 \times 10^{-08}}$	$\mathbf{3.01 \times 10^{-06}}$
Oatmeal (C)	4 to < 12 months	3.60×10^{-07}	5.38×10^{-09}	3.65×10^{-07}
	12 to < 24 months	1.13×10^{-06}	1.70×10^{-08}	1.15×10^{-06}
	ILCR	$\mathbf{1.49 \times 10^{-06}}$	$\mathbf{2.23 \times 10^{-08}}$	$\mathbf{1.52 \times 10^{-06}}$
Multi-grain cereal (D)	4 to < 12 months	7.35×10^{-07}	1.01×10^{-08}	7.45×10^{-07}
	12 to < 24 months	2.31×10^{-06}	3.19×10^{-08}	2.35×10^{-06}
	ILCR	$\mathbf{3.05 \times 10^{-06}}$	$\mathbf{4.21 \times 10^{-08}}$	$\mathbf{3.09 \times 10^{-06}}$
Rice and oat cereal (E)	4 to < 12 months	1.50×10^{-06}	1.95×10^{-08}	1.52×10^{-06}
	12 to < 24 months	4.74×10^{-06}	6.13×10^{-08}	4.80×10^{-06}
	ILCR	$\mathbf{6.24 \times 10^{-06}}$	$\mathbf{8.08 \times 10^{-08}}$	$\mathbf{6.32 \times 10^{-06}}$
Rice and oat cereal (F)	4 to < 12 months	7.01×10^{-06}	8.26×10^{-09}	7.02×10^{-06}
	12 to < 24 months	2.21×10^{-05}	2.60×10^{-08}	2.21×10^{-05}
	ILCR	$\mathbf{2.91 \times 10^{-05}}$	$\mathbf{3.43 \times 10^{-08}}$	$\mathbf{2.91 \times 10^{-05}}$
Rice cereal and fruits (G)	4 to < 12 months	5.20×10^{-06}	9.08×10^{-09}	5.21×10^{-06}
	12 to < 24 months	1.64×10^{-05}	2.86×10^{-08}	1.64×10^{-05}
	ILCR	$\mathbf{2.16 \times 10^{-05}}$	$\mathbf{3.77 \times 10^{-08}}$	$\mathbf{2.16 \times 10^{-05}}$
Rice cereal and maize starch (H)	4 to < 12 months	1.08×10^{-06}	7.31×10^{-09}	1.09×10^{-06}
	12 to < 24 months	3.41×10^{-06}	2.30×10^{-08}	3.43×10^{-06}
	ILCR	$\mathbf{4.49 \times 10^{-06}}$	$\mathbf{3.03 \times 10^{-08}}$	$\mathbf{4.52 \times 10^{-06}}$
Rice cereal and maize starch (I)	4 to < 12 months	9.74×10^{-07}	6.56×10^{-09}	9.81×10^{-07}
	12 to < 24 months	3.07×10^{-06}	2.07×10^{-08}	3.09×10^{-06}
	ILCR	$\mathbf{4.04 \times 10^{-06}}$	$\mathbf{2.72 \times 10^{-08}}$	$\mathbf{4.07 \times 10^{-06}}$
Rice cereal (J)	4 to < 12 months	6.48×10^{-06}	1.62×10^{-08}	6.50×10^{-06}
	12 to < 24 months	2.04×10^{-05}	5.10×10^{-08}	2.05×10^{-05}
	ILCR	$\mathbf{2.69 \times 10^{-05}}$	$\mathbf{6.72 \times 10^{-08}}$	$\mathbf{2.70 \times 10^{-05}}$
Rice cereal (K)	4 to < 12 months	6.49×10^{-06}	8.00×10^{-09}	6.50×10^{-06}
	12 to < 24 months	2.05×10^{-05}	2.52×10^{-08}	2.05×10^{-05}
	ILCR	$\mathbf{2.70 \times 10^{-05}}$	$\mathbf{3.32 \times 10^{-08}}$	$\mathbf{2.70 \times 10^{-05}}$
Rice cereal (L)	4 to < 12 months	7.18×10^{-06}	1.04×10^{-08}	7.19×10^{-06}
	12 to < 24 months	2.26×10^{-05}	3.27×10^{-08}	2.27×10^{-05}
	ILCR	$\mathbf{2.98 \times 10^{-05}}$	$\mathbf{4.31 \times 10^{-08}}$	$\mathbf{2.99 \times 10^{-05}}$
Rice cereal (M)	4 to < 12 months	8.36×10^{-06}	6.64×10^{-09}	8.36×10^{-06}
	12 to < 24 months	2.63×10^{-05}	2.09×10^{-08}	2.63×10^{-05}
	ILCR	$\mathbf{3.47 \times 10^{-05}}$	$\mathbf{2.76 \times 10^{-08}}$	$\mathbf{3.47 \times 10^{-05}}$
Rice cereal (N)	4 to < 12 months	5.85×10^{-06}	7.34×10^{-09}	5.86×10^{-06}
	12 to < 24 months	1.84×10^{-05}	2.31×10^{-08}	1.84×10^{-05}
	ILCR	$\mathbf{2.43 \times 10^{-05}}$	$\mathbf{3.05 \times 10^{-08}}$	$\mathbf{2.43 \times 10^{-05}}$
Rice cereal (O)	4 to < 12 months	9.60×10^{-06}	5.04×10^{-09}	9.61×10^{-06}
	12 to < 24 months	3.03×10^{-05}	1.59×10^{-08}	3.03×10^{-05}
	ILCR	$\mathbf{3.99 \times 10^{-05}}$	$\mathbf{2.09 \times 10^{-08}}$	$\mathbf{3.99 \times 10^{-05}}$
Rice cereal (P)	4 to < 12 months	4.95×10^{-06}	5.30×10^{-09}	4.96×10^{-06}
	12 to < 24 months	1.56×10^{-05}	1.67×10^{-08}	1.56×10^{-05}

	ILCR	**2.06×10^{-05}**	**2.20×10^{-08}**	**2.06×10^{-05}**
	4 to < 12 months	7.48×10^{-06}	1.07×10^{-08}	7.49×10^{-06}
Rice cereal (Q)	12 to < 24 months	2.36×10^{-05}	3.38×10^{-08}	2.36×10^{-05}
	ILCR	**3.10×10^{-05}**	**4.46×10^{-08}**	**3.11×10^{-05}**
	4 to < 12 months	8.73×10^{-07}	1.01×10^{-08}	8.83×10^{-07}
	12 to < 24 months	2.75×10^{-06}	3.19×10^{-08}	2.78×10^{-06}
Rice cereal (R)	**ILCR**	**3.62×10^{-06}**	**4.20×10^{-08}**	**3.66×10^{-06}**

Table S2 – Estimated average daily dose (ADD) associated with exposure to essential and non-essential elements present in different kinds of infant cereal.

			Essential elements (mg/kg-day)											Non-essential elements (mg/kg-day)			
Infant cereal	**ID**	**Age group**	**Ag**	**B**	**Ba**	**Co**	**Cr**	**Cu**	**Mn**	**Ni**	**Se**	**Sr**	**Zn**	**As**	**Al**	**Cd**	**Pb**
Corn cereal	A	4 to < 12 months	2.00×10^{-10}	2.00×10^{-10}	1.23×10^{-03}	2.58×10^{-05}	4.37×10^{-04}	4.85×10^{-03}	9.93×10^{-03}	3.09×10^{-04}	2.48×10^{-04}	2.48×10^{-02}	3.08×10^{-01}	1.90×10^{-05}	9.04×10^{-03}	3.07×10^{-06}	3.43×10^{-05}
		12 to < 24 months	4.20×10^{-10}	4.20×10^{-10}	2.59×10^{-03}	5.42×10^{-05}	9.19×10^{-04}	1.02×10^{-02}	2.08×10^{-02}	6.48×10^{-04}	5.21×10^{-04}	5.20×10^{-02}	6.47×10^{-01}	3.99×10^{-05}	1.90×10^{-02}	6.44×10^{-06}	7.21×10^{-05}
Oatmeal	B	4 to < 12 months	9.87×10^{-05}	5.40×10^{-04}	1.29×10^{-02}	1.18×10^{-04}	3.60×10^{-04}	1.07×10^{-02}	1.04×10^{-01}	1.99×10^{-03}	2.73×10^{-05}	2.94×10^{-02}	3.71×10^{-01}	5.01×10^{-05}	7.01×10^{-03}	6.33×10^{-06}	1.07×10^{-04}
		12 to < 24 months	2.07×10^{-04}	1.13×10^{-03}	2.71×10^{-02}	2.48×10^{-04}	7.57×10^{-04}	2.24×10^{-02}	2.18×10^{-01}	4.19×10^{-03}	5.74×10^{-05}	6.17×10^{-02}	7.80×10^{-01}	1.05×10^{-04}	1.47×10^{-02}	1.33×10^{-05}	2.24×10^{-04}
Oatmeal	C	4 to < 12 months	2.00×10^{-10}	2.00×10^{-10}	9.26×10^{-03}	4.68×10^{-05}	3.30×10^{-04}	1.36×10^{-02}	1.12×10^{-01}	1.67×10^{-03}	2.13×10^{-04}	2.74×10^{-02}	3.52×10^{-01}	2.52×10^{-05}	1.41×10^{-02}	7.40×10^{-06}	6.65×10^{-05}
		12 to < 24 months	4.20×10^{-10}	4.20×10^{-10}	1.94×10^{-02}	9.82×10^{-05}	6.93×10^{-04}	2.85×10^{-02}	2.35×10^{-01}	3.50×10^{-03}	4.48×10^{-04}	5.76×10^{-02}	7.39×10^{-01}	5.29×10^{-05}	2.95×10^{-02}	1.55×10^{-05}	1.40×10^{-04}
Multi-grain cereal	D	4 to < 12 months	2.00×10^{-10}	2.00×10^{-10}	5.08×10^{-03}	4.65×10^{-05}	4.72×10^{-04}	6.93×10^{-03}	3.23×10^{-02}	3.29×10^{-04}	1.48×10^{-04}	3.97×10^{-03}	5.32×10^{-01}	5.14×10^{-05}	1.12×10^{-02}	3.81×10^{-05}	1.25×10^{-04}
		12 to < 24 months	4.20×10^{-10}	4.20×10^{-10}	1.07×10^{-02}	9.76×10^{-05}	9.91×10^{-04}	1.45×10^{-02}	6.78×10^{-02}	6.91×10^{-04}	3.11×10^{-04}	8.34×10^{-03}	1.12×10^{00}	1.08×10^{-04}	2.35×10^{-02}	8.00×10^{-05}	2.63×10^{-04}
Rice and oat cereal	E	4 to < 12 months	4.19×10^{-05}	3.28×10^{-03}	2.32×10^{-03}	5.79×10^{-05}	1.36×10^{-03}	1.18×10^{-02}	6.45×10^{-02}	1.67×10^{-03}	3.02×10^{-03}	3.19×10^{-05}	1.63×10^{-01}	1.05×10^{-04}	3.52×10^{-02}	1.37×10^{-05}	2.41×10^{-04}
		12 to < 24 months	8.79×10^{-05}	6.89×10^{-03}	4.87×10^{-03}	1.22×10^{-04}	2.85×10^{-03}	2.47×10^{-02}	1.35×10^{-01}	3.50×10^{-03}	6.33×10^{-03}	6.71×10^{-05}	3.43×10^{-01}	2.21×10^{-04}	7.39×10^{-02}	2.88×10^{-05}	5.05×10^{-04}
Rice and oat cereal	F	4 to < 12 months	4.72×10^{-05}	5.71×10^{-04}	4.41×10^{-03}	7.94×10^{-05}	1.98×10^{-04}	6.34×10^{-03}	4.14×10^{-02}	7.29×10^{-04}	1.24×10^{-04}	1.91×10^{-01}	2.67×10^{-01}	4.91×10^{-04}	1.55×10^{-02}	5.19×10^{-05}	1.02×10^{-04}
		12 to < 24 months	9.91×10^{-05}	1.20×10^{-03}	9.25×10^{-03}	1.67×10^{-04}	4.16×10^{-04}	1.33×10^{-02}	8.69×10^{-02}	1.53×10^{-03}	2.61×10^{-04}	4.02×10^{-01}	5.61×10^{-01}	1.03×10^{-03}	3.25×10^{-02}	1.09×10^{-04}	2.14×10^{-04}
Rice cereal and fruits	G	4 to < 12 months	1.29×10^{-04}	7.63×10^{-03}	4.85×10^{-03}	2.45×10^{-04}	8.38×10^{-04}	1.69×10^{-02}	5.29×10^{-02}	1.43×10^{-03}	1.80×10^{-04}	1.30×10^{-02}	6.40×10^{-02}	3.64×10^{-04}	1.89×10^{-02}	5.71×10^{-05}	1.12×10^{-04}
		12 to < 24 months	2.70×10^{-04}	1.60×10^{-02}	1.02×10^{-02}	5.14×10^{-04}	1.76×10^{-03}	3.55×10^{-02}	1.11×10^{-01}	3.01×10^{-03}	3.79×10^{-04}	2.73×10^{-02}	1.34×10^{-01}	7.64×10^{-04}	3.97×10^{-02}	1.20×10^{-04}	2.36×10^{-04}
Rice cereal and maize starch	H	4 to < 12 months	2.00×10^{-10}	2.00×10^{-10}	1.66×10^{-03}	5.79×10^{-05}	1.53×10^{-03}	1.25×10^{-02}	5.28×10^{-02}	1.94×10^{-03}	1.94×10^{-04}	6.61×10^{-02}	2.69×10^{-01}	7.57×10^{-05}	1.87×10^{-02}	1.73×10^{-05}	9.03×10^{-05}
		12 to < 24 months	4.20×10^{-10}	4.20×10^{-10}	3.48×10^{-03}	1.21×10^{-04}	3.22×10^{-03}	2.62×10^{-02}	1.11×10^{-01}	4.07×10^{-03}	4.08×10^{-04}	1.39×10^{-01}	5.64×10^{-01}	1.59×10^{-04}	3.92×10^{-02}	3.64×10^{-05}	1.90×10^{-04}
Rice cereal and maize starch	I	4 to < 12 months	2.00×10^{-10}	2.00×10^{-10}	1.42×10^{-05}	2.12×10^{-05}	5.56×10^{-04}	8.10×10^{-04}	4.09×10^{-03}	3.23×10^{-04}	1.90×10^{-04}	3.41×10^{-04}	4.35×10^{-01}	6.82×10^{-05}	5.06×10^{-03}	1.22×10^{-05}	8.10×10^{-05}
		12 to < 24 months	4.20×10^{-10}	4.20×10^{-10}	2.99×10^{-05}	4.45×10^{-05}	1.17×10^{-03}	1.70×10^{-03}	8.59×10^{-03}	6.77×10^{-04}	3.99×10^{-04}	7.15×10^{-04}	9.14×10^{-01}	1.43×10^{-04}	1.06×10^{-02}	2.57×10^{-05}	1.70×10^{-04}
Rice cereal	J	4 to < 12 months	2.00×10^{-10}	2.00×10^{-10}	1.21×10^{-03}	4.77×10^{-05}	3.75×10^{-04}	6.92×10^{-03}	2.81×10^{-02}	6.93×10^{-04}	1.08×10^{-04}	1.86×10^{-02}	2.79×10^{-01}	4.54×10^{-04}	9.64×10^{-03}	8.26×10^{-06}	2.00×10^{-04}

		12 to < 24 months	4.20×10^{-10}	4.20×10^{-10}	2.55×10^{-03}	1.00×10^{-04}	7.88×10^{-04}	1.45×10^{-02}	5.90×10^{-02}	1.46×10^{-03}	2.26×10^{-04}	3.91×10^{-02}	5.86×10^{-01}	9.53×10^{-04}	2.02×10^{-02}	1.74×10^{-05}	4.20×10^{-04}
Rice cereal	K	4 to < 12 months	8.65×10^{-05}	2.00×10^{-10}	1.35×10^{-03}	9.34×10^{-05}	2.86×10^{-04}	8.21×10^{-03}	4.12×10^{-02}	8.83×10^{-04}	4.01×10^{-03}	1.30×10^{-04}	4.86×10^{-01}	4.55×10^{-04}	2.00×10^{-10}	6.86×10^{-05}	9.88×10^{-05}
		12 to < 24 months	1.82×10^{-04}	4.20×10^{-10}	2.83×10^{-03}	1.96×10^{-04}	6.00×10^{-04}	1.72×10^{-02}	8.66×10^{-02}	1.85×10^{-03}	8.41×10^{-03}	2.72×10^{-04}	1.02×10^{00}	9.55×10^{-04}	4.20×10^{-10}	1.44×10^{-04}	2.08×10^{-04}
Rice cereal	L	4 to < 12 months	2.00×10^{-10}	2.00×10^{-10}	8.58×10^{-04}	1.11×10^{-04}	2.42×10^{-04}	8.79×10^{-03}	4.59×10^{-02}	6.88×10^{-04}	1.31×10^{-04}	3.10×10^{-03}	5.07×10^{-01}	5.03×10^{-04}	2.21×10^{-03}	7.65×10^{-05}	1.28×10^{-04}
		12 to < 24 months	4.20×10^{-10}	4.20×10^{-10}	1.80×10^{-03}	2.34×10^{-04}	5.07×10^{-04}	1.85×10^{-02}	9.65×10^{-02}	1.45×10^{-03}	2.76×10^{-04}	6.51×10^{-03}	1.07×10^{00}	1.06×10^{-03}	4.64×10^{-03}	1.61×10^{-04}	2.69×10^{-04}
Rice cereal	M	4 to < 12 months	1.32×10^{-04}	1.24×10^{-03}	2.27×10^{-03}	7.06×10^{-05}	1.07×10^{-03}	7.55×10^{-03}	5.64×10^{-02}	7.33×10^{-04}	1.12×10^{-04}	4.51×10^{-03}	4.98×10^{-01}	5.85×10^{-04}	3.25×10^{-04}	8.86×10^{-05}	8.21×10^{-05}
		12 to < 24 months	2.76×10^{-04}	2.61×10^{-03}	4.76×10^{-03}	1.48×10^{-04}	2.24×10^{-03}	1.59×10^{-02}	1.18×10^{-01}	1.54×10^{-03}	2.36×10^{-04}	9.48×10^{-03}	1.05×10^{00}	1.23×10^{-03}	6.83×10^{-04}	1.86×10^{-04}	1.72×10^{-04}
Rice cereal	N	4 to < 12 months	1.10×10^{-04}	4.25×10^{-03}	5.92×10^{-04}	9.82×10^{-05}	2.80×10^{-04}	7.82×10^{-03}	3.63×10^{-02}	4.51×10^{-04}	1.91×10^{-04}	4.93×10^{-04}	4.59×10^{-01}	4.09×10^{-04}	2.00×10^{-10}	5.55×10^{-05}	9.07×10^{-05}
		12 to < 24 months	2.30×10^{-04}	8.92×10^{-03}	1.24×10^{-03}	2.06×10^{-04}	5.88×10^{-04}	1.64×10^{-02}	7.63×10^{-02}	9.47×10^{-04}	4.02×10^{-04}	1.04×10^{-03}	9.64×10^{-01}	8.60×10^{-04}	4.20×10^{-10}	1.17×10^{-04}	1.90×10^{-04}
Rice cereal	O	4 to < 12 months	2.59×10^{-04}	2.00×10^{-10}	1.69×10^{-03}	2.99×10^{-04}	7.21×10^{-04}	1.17×10^{-02}	6.05×10^{-02}	1.06×10^{-03}	2.14×10^{-04}	7.09×10^{-04}	4.28×10^{-01}	6.72×10^{-04}	3.46×10^{-03}	7.48×10^{-05}	6.23×10^{-05}
		12 to < 24 months	5.43×10^{-04}	4.20×10^{-10}	3.55×10^{-03}	6.28×10^{-04}	1.51×10^{-03}	2.46×10^{-02}	1.27×10^{-01}	2.23×10^{-03}	4.49×10^{-04}	1.49×10^{-03}	8.98×10^{-01}	1.41×10^{-03}	7.27×10^{-03}	1.57×10^{-04}	1.31×10^{-04}
Rice cereal	P	4 to < 12 months	6.80×10^{-05}	6.29×10^{-03}	4.77×10^{-03}	2.18×10^{-04}	8.47×10^{-04}	1.72×10^{-02}	5.77×10^{-02}	1.73×10^{-03}	1.71×10^{-04}	1.58×10^{-02}	2.31×10^{-01}	3.47×10^{-04}	1.98×10^{-02}	4.34×10^{-05}	6.55×10^{-05}
		12 to < 24 months	1.43×10^{-04}	1.32×10^{-02}	1.00×10^{-02}	4.58×10^{-04}	1.78×10^{-03}	3.61×10^{-02}	1.21×10^{-01}	3.64×10^{-03}	3.59×10^{-04}	3.33×10^{-02}	4.85×10^{-01}	7.28×10^{-04}	4.17×10^{-02}	9.12×10^{-05}	1.38×10^{-04}
Rice cereal	Q	4 to < 12 months	1.94×10^{-04}	2.00×10^{-10}	1.77×10^{-03}	1.33×10^{-04}	1.53×10^{-04}	1.15×10^{-02}	3.98×10^{-02}	8.60×10^{-04}	5.42×10^{-05}	2.77×10^{-02}	2.14×10^{-01}	5.23×10^{-04}	1.42×10^{-02}	5.01×10^{-05}	1.33×10^{-04}
		12 to < 24 months	4.08×10^{-04}	4.20×10^{-10}	3.71×10^{-03}	2.79×10^{-04}	3.22×10^{-04}	2.41×10^{-02}	8.36×10^{-02}	1.81×10^{-03}	1.14×10^{-04}	5.82×10^{-02}	4.49×10^{-01}	1.10×10^{-03}	2.98×10^{-02}	1.05×10^{-04}	2.79×10^{-04}
Rice cereal	R	4 to < 12 months	4.38×10^{-06}	2.00×10^{-10}	2.25×10^{-04}	5.92×10^{-05}	8.45×10^{-04}	1.34×10^{-03}	6.47×10^{-03}	3.12×10^{-04}	3.31×10^{-03}	2.09×10^{-05}	5.21×10^{-01}	6.11×10^{-05}	2.00×10^{-10}	9.17×10^{-06}	1.25×10^{-04}
		12 to < 24 months	9.20×10^{-06}	4.20×10^{-10}	4.72×10^{-04}	1.24×10^{-04}	1.77×10^{-03}	2.81×10^{-03}	1.36×10^{-02}	6.55×10^{-04}	6.95×10^{-03}	4.38×10^{-05}	1.09×10^{00}	1.28×10^{-04}	4.20×10^{-10}	1.93×10^{-05}	2.62×10^{-04}

Table S3 – Estimated incremental lifetime cancer risk (ILCR) associated with exposure to non-essential elements present in different kinds of infant cereal for a proportion of iAs of 52%.

Infant cereal	ID	iAs	Pb	Total
Corn cereal	A	5.86×10^{-07}	1.15×10^{-08}	6.31×10^{-07}
Oatmeal	B	1.55×10^{-06}	3.58×10^{-08}	1.67×10^{-06}
Oatmeal	C	7.76×10^{-07}	2.23×10^{-08}	8.43×10^{-07}
Multi-grain cereal	D	1.59×10^{-06}	4.21×10^{-08}	1.72×10^{-06}
Rice and oat cereal	E	3.25×10^{-06}	8.08×10^{-08}	3.51×10^{-06}
Rice and oat cereal	F	1.51×10^{-05}	3.43×10^{-08}	1.60×10^{-05}
Rice cereal and fruits	G	1.12×10^{-05}	3.77×10^{-08}	1.19×10^{-05}
Rice cereal and maize starch	H	2.33×10^{-06}	3.03×10^{-08}	2.50×10^{-06}
Rice cereal and maize starch	I	2.10×10^{-06}	2.72×10^{-08}	2.25×10^{-06}
Rice cereal	J	1.40×10^{-05}	6.72×10^{-08}	1.49×10^{-05}
Rice cereal	K	1.40×10^{-05}	3.32×10^{-08}	1.49×10^{-05}
Rice cereal	L	1.55×10^{-05}	4.31×10^{-08}	1.64×10^{-05}
Rice cereal	M	1.80×10^{-05}	2.76×10^{-08}	1.91×10^{-05}
Rice cereal	N	1.26×10^{-05}	3.05×10^{-08}	1.34×10^{-05}
Rice cereal	O	2.07×10^{-05}	2.09×10^{-08}	2.19×10^{-05}
Rice cereal	P	1.07×10^{-05}	2.20×10^{-08}	1.13×10^{-05}
Rice cereal	Q	1.61×10^{-05}	4.46×10^{-08}	1.71×10^{-05}
Rice cereal	R	1.88×10^{-06}	4.20×10^{-08}	2.03×10^{-06}

Table S4 – Fractional Hazard Quotient (HQ) and lifetime HQ of exposure to essential and non-essential elements present in infant cereal with the results of HQ>1 highlighted

Infant cereal	ID	Age group	Essential elements: Ag	B	Ba	Co	Cr	Cu	Mn	Ni	Se	Sr	Zn	Non-essential elements: As	Al	Cd	Pb
		4 to <12 months	1.60×10^{-08}	4.00×10^{-10}	2.5×10^{-03}	1.0×10^{-03}	1.2×10^{-04}	1.9×10^{-01}	1.3×10^{-01}	1.1×10^{-02}	2.0×10^{-02}	1.7×10^{-02}	4.1×10^{-01}	2.5×10^{-02}	3.6×10^{-03}	1.1×10^{-01}	3.9×10^{-03}
		12 to <24 months	5.04×10^{-08}	1.26×10^{-09}	7.8×10^{-03}	3.3×10^{-03}	3.7×10^{-04}	6.1×10^{-01}	4.2×10^{-01}	3.5×10^{-02}	6.3×10^{-02}	5.2×10^{-02}	1.3×10^{00}	8.0×10^{-02}	1.1×10^{-02}	3.5×10^{-01}	1.2×10^{-02}
Corn cereal	A	**4 to < 24 months**	**6.64×10^{-08}**	1.66×10^{-09}	**1.0×10^{-02}**	**4.3×10^{-03}**	**4.8×10^{-04}**	**8.1×10^{-01}**	**5.5×10^{-01}**	**4.7×10^{-02}**	**8.2×10^{-02}**	**6.9×10^{-02}**	**1.7×10^{00}**	**1.1×10^{-01}**	**1.5×10^{-02}**	**4.6×10^{-01}**	**1.6×10^{-02}**
		0.5 to 1 year	7.90×10^{-03}	1.08×10^{-03}	2.6×10^{-02}	4.7×10^{-03}	9.6×10^{-05}	4.3×10^{-01}	1.4×10^{00}	7.3×10^{-02}	2.2×10^{-03}	2.0×10^{-02}	5.0×10^{-01}	6.7×10^{-02}	2.8×10^{-03}	2.3×10^{-01}	1.2×10^{-02}
		1 to 2 years	2.49×10^{-02}	3.40×10^{-03}	8.1×10^{-02}	1.5×10^{-02}	3.0×10^{-04}	1.3×10^{00}	4.4×10^{00}	2.3×10^{-01}	6.9×10^{-03}	6.2×10^{-02}	1.6×10^{00}	2.1×10^{-01}	8.8×10^{-03}	7.2×10^{-01}	3.8×10^{-02}
Oatmeal	B	**4 to < 24 months**	**3.28×10^{-02}**	4.48×10^{-03}	**1.1×10^{-01}**	**2.0×10^{-02}**	**4.0×10^{-04}**	**1.8×10^{00}**	**5.7×10^{00}**	**3.0×10^{-01}**	**9.1×10^{-03}**	**8.1×10^{-02}**	**2.1×10^{00}**	**2.8×10^{-01}**	**1.2×10^{-02}**	**9.5×10^{-01}**	**5.1×10^{-02}**
		0.5 to 1 year	1.60×10^{-08}	4.00×10^{-10}	1.9×10^{-02}	1.9×10^{-03}	8.8×10^{-05}	5.4×10^{-01}	1.5×10^{00}	6.1×10^{-02}	1.7×10^{-02}	1.8×10^{-02}	4.7×10^{-01}	3.4×10^{-02}	5.6×10^{-03}	2.7×10^{-01}	7.6×10^{-03}
		1 to 2 years	5.04×10^{-08}	1.26×10^{-09}	5.8×10^{-02}	5.9×10^{-03}	2.8×10^{-04}	1.7×10^{00}	4.7×10^{00}	1.9×10^{-01}	5.4×10^{-02}	5.8×10^{-02}	1.5×10^{00}	1.1×10^{-01}	1.8×10^{-02}	8.5×10^{-01}	2.4×10^{-02}
Oatmeal	C	**4 to < 24 months**	**6.64×10^{-08}**	1.66×10^{-09}	**7.7×10^{-02}**	**7.8×10^{-03}**	**3.7×10^{-04}**	**2.3×10^{00}**	**6.2×10^{00}**	**2.5×10^{-01}**	**7.1×10^{-02}**	**7.6×10^{-02}**	**1.9×10^{00}**	**1.4×10^{-01}**	**2.3×10^{-02}**	**1.1×10^{00}**	**3.2×10^{-02}**
		0.5 to 1 year	1.60×10^{-08}	4.00×10^{-10}	1.0×10^{-02}	1.9×10^{-03}	1.3×10^{-04}	2.8×10^{-01}	4.3×10^{-01}	1.2×10^{-02}	1.2×10^{-02}	2.6×10^{-03}	7.1×10^{-01}	6.9×10^{-02}	4.48×10^{-03}	1.4×10^{00}	1.4×10^{-02}
		1 to 2 years	5.04×10^{-08}	1.26×10^{-09}	3.2×10^{-02}	5.9×10^{-03}	4.0×10^{-04}	8.7×10^{-01}	1.4×10^{00}	3.8×10^{-02}	3.7×10^{-02}	8.3×10^{-03}	2.2×10^{00}	2.2×10^{-01}	1.41×10^{-02}	4.4×10^{00}	4.5×10^{-02}
Wheat, corn and rice cereal	D	**4 to < 24 months**	**6.64×10^{-08}**	1.66×10^{-09}	**4.2×10^{-02}**	**7.7×10^{-03}**	**5.2×10^{-04}**	**1.1×10^{00}**	**1.8×10^{00}**	**5.0×10^{-02}**	**4.9×10^{-02}**	**1.1×10^{-02}**	**2.9×10^{00}**	**2.8×10^{-01}**	**1.86×10^{-02}**	**5.7×10^{00}**	**5.9×10^{-02}**
		0.5 to 1 year	3.35×10^{-03}	6.57×10^{-03}	4.6×10^{-03}	2.3×10^{-03}	3.6×10^{-04}	4.7×10^{-01}	8.6×10^{-01}	6.1×10^{-02}	2.4×10^{-01}	2.1×10^{-05}	2.2×10^{-01}	1.4×10^{-01}	1.41×10^{-02}	5.0×10^{-01}	2.7×10^{-02}
		1 to 2 years	1.05×10^{-02}	2.07×10^{-02}	1.5×10^{-02}	7.3×10^{-03}	1.1×10^{-03}	1.5×10^{00}	2.7×10^{00}	1.9×10^{-01}	7.6×10^{-01}	6.7×10^{-05}	6.9×10^{-01}	4.4×10^{-01}	4.44×10^{-02}	1.6×10^{00}	8.7×10^{-02}
Rice and oat cereal	E	**4 to < 24 months**	**1.39×10^{-02}**	2.73×10^{-02}	**1.9×10^{-02}**	**9.6×10^{-03}**	**1.5×10^{-03}**	**2.0×10^{00}**	**3.6×10^{00}**	**2.5×10^{-01}**	**1.0×10^{00}**	**8.8×10^{-05}**	**9.0×10^{-01}**	**5.8×10^{-01}**	**5.84×10^{-02}**	**2.1×10^{00}**	**1.1×10^{-01}**
		0.5 to 1 year	3.77×10^{-03}	1.14×10^{-03}	8.81×10^{-03}	3.18×10^{-03}	5.3×10^{-05}	2.5×10^{-01}	5.5×10^{-01}	2.6×10^{-02}	9.9×10^{-03}	1.3×10^{-01}	3.6×10^{-01}	6.5×10^{-01}	6.19×10^{-03}	1.9×10^{00}	1.2×10^{-02}
		1 to 2 years	1.19×10^{-02}	3.59×10^{-03}	2.78×10^{-02}	1.00×10^{-02}	1.7×10^{-04}	8.0×10^{-01}	1.7×10^{00}	8.3×10^{-02}	3.1×10^{-02}	4.0×10^{-01}	1.1×10^{00}	2.1×10^{00}	2.0×10^{-02}	5.9×10^{00}	3.7×10^{-02}
Rice and oat cereal	F	**4 to < 24 months**	**1.57×10^{-02}**	4.74×10^{-03}	**3.66×10^{-02}**	**1.32×10^{-02}**	**2.2×10^{-04}**	**1.1×10^{00}**	**2.3×10^{00}**	**1.1×10^{-01}**	**4.1×10^{-02}**	**5.3×10^{-01}**	**1.5×10^{00}**	**2.7×10^{00}**	**2.6×10^{-02}**	**7.8×10^{00}**	**4.8×10^{-02}**
		0.5 to 1 year	1.03×10^{-02}	1.53×10^{-02}	9.70×10^{-03}	9.79×10^{-03}	2.2×10^{-04}	6.8×10^{-01}	7.1×10^{-01}	5.2×10^{-02}	1.4×10^{-02}	8.7×10^{-03}	8.5×10^{-02}	4.9×10^{-01}	7.6×10^{-03}	2.1×10^{00}	1.3×10^{-02}
		1 to 2 years	3.24×10^{-02}	4.81×10^{-02}	3.05×10^{-02}	3.09×10^{-02}	7.0×10^{-04}	2.1×10^{00}	2.2×10^{00}	1.6×10^{-01}	4.5×10^{-02}	2.7×10^{-02}	2.7×10^{-01}	1.5×10^{00}	2.4×10^{-02}	6.5×10^{00}	4.0×10^{-02}
Rice cereal and fruits	G	**4 to < 24 months**	**4.27×10^{-02}**	6.34×10^{-02}	**4.02×10^{-02}**	**4.06×10^{-02}**	**9.3×10^{-04}**	**2.8×10^{00}**	**2.9×10^{00}**	**2.2×10^{-01}**	**6.0×10^{-02}**	**3.6×10^{-02}**	**3.5×10^{-01}**	**2.0×10^{00}**	**3.1×10^{-02}**	**8.6×10^{00}**	**5.3×10^{-02}**
Rice cereal and		0.5 to 1 year	1.60×10^{-08}	4.00×10^{-10}	3.32×10^{-03}	2.31×10^{-03}	4.1×10^{-04}	5.0×10^{-01}	7.0×10^{-01}	7.0×10^{-02}	1.6×10^{-02}	4.4×10^{-02}	3.6×10^{-01}	1.0×10^{-01}	7.5×10^{-03}	6.3×10^{-01}	1.0×10^{-02}

maize starch		1 to 2 years	5.04×10^{-08}	1.26×10^{-09}	1.04×10^{-02}	7.29×10^{-03}	1.3×10^{-03}	1.6×10^{00}	2.2×10^{00}	2.2×10^{-01}	4.9×10^{-02}	1.4×10^{-01}	1.1×10^{00}	3.2×10^{-01}	2.4×10^{-02}	2.0×10^{00}	3.3×10^{-02}
	H	**4 to < 24 months**	**6.64×10^{-08}**	1.66×10^{-09}	**1.38×10^{-02}**	**9.60×10^{-03}**	**1.7×10^{-03}**	**2.1×10^{00}**	**2.9×10^{00}**	**2.9×10^{-01}**	**6.5×10^{-02}**	**1.8×10^{-01}**	**1.5×10^{00}**	**4.2×10^{-01}**	**3.1×10^{-02}**	**2.6×10^{00}**	**4.3×10^{-02}**
		0.5 to 1 year	1.60×10^{-08}	4.00×10^{-10}	2.85×10^{-05}	8.48×10^{-04}	1.5×10^{-04}	3.2×10^{-02}	5.5×10^{-02}	1.2×10^{-02}	1.5×10^{-02}	2.3×10^{-04}	5.8×10^{-01}	9.1×10^{-02}	2.0×10^{-03}	4.4×10^{-01}	9.3×10^{-03}
		1 to 2 years	5.04×10^{-08}	1.26×10^{-09}	8.96×10^{-05}	2.67×10^{-03}	4.7×10^{-04}	1.0×10^{-01}	1.7×10^{-01}	3.7×10^{-02}	4.8×10^{-02}	7.2×10^{-04}	1.8×10^{00}	2.9×10^{-01}	6.4×10^{-03}	1.4×10^{00}	2.9×10^{-02}
Rice cereal and maize starch	I	**4 to < 24 months**	**6.64×10^{-08}**	1.66×10^{-09}	**1.18×10^{-04}**	**3.52×10^{-03}**	**6.2×10^{-04}**	**1.3×10^{-01}**	**2.3×10^{-01}**	**4.9×10^{-02}**	**6.3×10^{-02}**	**9.4×10^{-04}**	**2.4×10^{00}**	**3.8×10^{-01}**	**8.4×10^{-03}**	**1.8×10^{00}**	**3.8×10^{-02}**
		0.5 to 1 year	1.60×10^{-08}	4.00×10^{-10}	2.43×10^{-03}	1.91×10^{-03}	1.00×10^{-04}	2.77×10^{-01}	3.75×10^{-01}	2.52×10^{-02}	8.61×10^{-03}	1.24×10^{-02}	3.72×10^{-01}	6.05×10^{-01}	3.9×10^{-03}	3.00×10^{-01}	2.28×10^{-02}
		1 to 2 years	5.04×10^{-08}	1.26×10^{-09}	7.64×10^{-03}	6.01×10^{-03}	3.15×10^{-04}	8.72×10^{-01}	1.18×10^{00}	7.94×10^{-02}	2.71×10^{-02}	3.91×10^{-02}	1.17×10^{00}	1.91×10^{00}	1.2×10^{-02}	9.47×10^{-01}	7.20×10^{-02}
Rice cereal	J	**4 to < 24 months**	**6.64×10^{-08}**	**1.66×10^{-09}**	**1.01×10^{-02}**	**7.92×10^{-03}**	**4.16×10^{-04}**	**1.15×10^{00}**	**1.55×10^{00}**	**1.05×10^{-01}**	**3.57×10^{-02}**	**5.15×10^{-02}**	**1.54×10^{00}**	**2.51×10^{00}**	**1.60×10^{-02}**	**1.25×10^{00}**	**9.48×10^{-02}**
		0.5 to 1 year	6.92×10^{-03}	4.00×10^{-10}	2.69×10^{-03}	3.73×10^{-03}	7.62×10^{-05}	3.29×10^{-01}	5.50×10^{-01}	3.21×10^{-02}	3.20×10^{-01}	8.64×10^{-05}	6.48×10^{-01}	6.06×10^{-01}	8.00E-11	2.49×10^{00}	1.13×10^{-02}
		1 to 2 years	2.18×10^{-02}	1.26×10^{-09}	8.48×10^{-03}	1.18×10^{-02}	2.40×10^{-04}	1.03×10^{00}	1.73×10^{00}	1.01×10^{-01}	1.01×10^{00}	2.72×10^{-04}	2.04×10^{00}	1.91×10^{00}	2.52×10^{-10}	7.85×10^{00}	3.56×10^{-02}
Rice cereal	K	**4 to < 24 months**	**2.87×10^{-02}**	**1.66×10^{-09}**	**1.12×10^{-02}**	**1.55×10^{-02}**	**3.16×10^{-04}**	**1.36×10^{00}**	**2.28×10^{00}**	**1.33×10^{-01}**	**1.33×10^{00}**	**3.59×10^{-04}**	**2.69×10^{00}**	**2.52×10^{00}**	**3.32×10^{-10}**	**1.03×10^{01}**	**4.69×10^{-02}**
		0.5 to 1 year	1.60×10^{-08}	4.00×10^{-10}	1.72×10^{-03}	4.45×10^{-03}	6.44×10^{-05}	3.52×10^{-01}	6.13×10^{-01}	2.50×10^{-02}	1.05×10^{-02}	2.07×10^{-03}	6.77×10^{-01}	6.70×10^{-01}	8.83×10^{-04}	2.78×10^{00}	1.46×10^{-02}
		1 to 2 years	5.04×10^{-08}	1.26×10^{-09}	5.40×10^{-03}	1.40×10^{-02}	2.03×10^{-04}	1.11×10^{00}	1.93×10^{00}	7.88×10^{-02}	3.31×10^{-02}	6.51×10^{-03}	2.13×10^{00}	2.11×10^{00}	2.78×10^{-03}	8.77×10^{00}	4.61×10^{-02}
Rice cereal	L	**4 to < 24 months**	**6.64×10^{-08}**	**1.66×10^{-09}**	**7.12×10^{-03}**	**1.85×10^{-02}**	**2.67×10^{-04}**	**1.46×10^{00}**	**2.54×10^{00}**	**1.04×10^{-01}**	**4.36×10^{-02}**	**8.58×10^{-03}**	**2.81×10^{00}**	**2.78×10^{00}**	**3.67×10^{-03}**	**1.16×10^{01}**	**6.08×10^{-02}**
		0.5 to 1 year	1.05×10^{-02}	2.48×10^{-03}	4.54×10^{-03}	2.82×10^{-03}	2.84×10^{-04}	3.02×10^{-01}	7.52×10^{-01}	2.67×10^{-02}	8.99×10^{-03}	3.01×10^{-03}	6.64×10^{-01}	7.80×10^{-01}	1.30×10^{-04}	3.22×10^{00}	9.38×10^{-03}
		1 to 2 years	3.32×10^{-02}	7.83×10^{-03}	1.43×10^{-02}	8.90×10^{-03}	8.96×10^{-04}	9.52×10^{-01}	2.37×10^{00}	8.40×10^{-02}	2.83×10^{-02}	9.48×10^{-03}	2.09×10^{00}	2.46×10^{00}	4.10×10^{-04}	1.01×10^{01}	2.95×10^{-02}
Rice cereal	M	**4 to < 24 months**	**4.37×10^{-02}**	**1.03×10^{-02}**	**1.88×10^{-02}**	**1.17×10^{-02}**	**1.18×10^{-03}**	**1.25×10^{00}**	**3.12×10^{00}**	**1.11×10^{-01}**	**3.73×10^{-02}**	**1.25×10^{-02}**	**2.75×10^{00}**	**3.24×10^{00}**	**5.40×10^{-04}**	**1.34×10^{01}**	**3.89×10^{-02}**
		0.5 to 1 year	8.77×10^{-03}	8.50×10^{-03}	1.18×10^{-03}	3.93×10^{-03}	7.46×10^{-05}	3.13×10^{-01}	4.84×10^{-01}	1.64×10^{-02}	1.53×10^{-02}	3.29×10^{-04}	6.12×10^{-01}	5.46×10^{-01}	8.00E-11	2.02×10^{00}	1.04×10^{-02}
		1 to 2 years	2.76×10^{-02}	2.68×10^{-02}	3.73×10^{-03}	1.24×10^{-02}	2.35×10^{-04}	9.85×10^{-01}	1.53×10^{00}	5.17×10^{-02}	4.82×10^{-02}	1.04×10^{-03}	1.93×10^{00}	1.72×10^{00}	2.52×10^{-10}	6.36×10^{00}	3.26×10^{-02}
Rice cereal	N	**4 to < 24 months**	**3.64×10^{-02}**	**3.53×10^{-02}**	**4.91×10^{-03}**	**1.63×10^{-02}**	**3.10×10^{-04}**	**1.30×10^{00}**	**2.01×10^{00}**	**6.81×10^{-02}**	**6.35×10^{-02}**	**1.36×10^{-03}**	**2.54×10^{00}**	**2.27×10^{00}**	**3.32×10^{-10}**	**8.37×10^{00}**	**4.30×10^{-02}**
		0.5 to 1 year	2.07×10^{-02}	4.00×10^{-10}	3.38×10^{-03}	1.20×10^{-02}	1.92×10^{-04}	4.69×10^{-01}	8.07×10^{-01}	3.85×10^{-02}	1.71×10^{-02}	4.73×10^{-04}	5.70×10^{-01}	8.96×10^{-01}	1.38×10^{-03}	2.72×10^{00}	7.12×10^{-03}
		1 to 2 years	6.51×10^{-02}	1.26×10^{-09}	1.07×10^{-02}	3.77×10^{-02}	6.06×10^{-04}	1.48×10^{00}	2.54×10^{00}	1.21×10^{-01}	5.39×10^{-02}	1.49×10^{-03}	1.80×10^{00}	2.82×10^{00}	4.36×10^{-03}	8.57×10^{00}	2.24×10^{-02}
Rice cereal	O	**4 to < 24 months**	**8.58×10^{-02}**	**1.66×10^{-09}**	**1.40×10^{-02}**	**4.96×10^{-02}**	**7.98×10^{-04}**	**1.94×10^{00}**	**3.35×10^{00}**	**1.60×10^{-01}**	**7.10×10^{-02}**	**1.96×10^{-03}**	**2.37×10^{00}**	**3.72×10^{00}**	**5.75×10^{-03}**	**1.13×10^{01}**	**2.96×10^{-02}**
		0.5 to 1 year	5.44×10^{-03}	1.26×10^{-02}	9.54×10^{-03}	8.73×10^{-03}	2.26×10^{-04}	6.88×10^{-01}	7.69×10^{-01}	6.30×10^{-02}	1.37×10^{-02}	1.06×10^{-02}	3.08×10^{-01}	4.62×10^{-01}	7.94×10^{-03}	1.58×10^{00}	7.48×10^{-03}
		1 to 2 years	1.71×10^{-02}	3.96×10^{-02}	3.00×10^{-02}	2.75×10^{-02}	7.11×10^{-04}	2.17×10^{00}	2.42×10^{00}	1.98×10^{-01}	4.30×10^{-02}	3.33×10^{-02}	9.70×10^{-01}	1.46×10^{00}	2.50×10^{-02}	4.97×10^{00}	2.36×10^{-02}
Rice cereal	P	**4 to < 24 months**	**2.26×10^{-02}**	**5.22×10^{-02}**	**3.96×10^{-02}**	**3.62×10^{-02}**	**9.37×10^{-04}**	**2.85×10^{00}**	**3.19×10^{00}**	**2.61×10^{-01}**	**5.67×10^{-02}**	**4.38×10^{-02}**	**1.28×10^{00}**	**1.92×10^{00}**	**3.29×10^{-02}**	**6.55×10^{00}**	**3.11×10^{-02}**

		0.5 to 1 year	1.55×10^{-02}	4.00×10^{-10}	3.53×10^{-03}	5.31×10^{-03}	4.09×10^{-05}	4.59×10^{-01}	5.31×10^{-01}	3.13×10^{-02}	4.33×10^{-03}	1.85×10^{-02}	2.85×10^{-01}	6.98×10^{-01}	5.68×10^{-03}	1.82×10^{00}	1.52×10^{-02}
		1 to 2 years	4.90×10^{-02}	1.26×10^{-09}	1.11×10^{-02}	1.67×10^{-02}	1.29×10^{-04}	1.44×10^{00}	1.67×10^{00}	9.85×10^{-02}	1.36×10^{-02}	5.82×10^{-02}	8.98×10^{-01}	2.20×10^{00}	1.79×10^{-02}	5.74×10^{00}	4.78×10^{-02}
Rice cereal	Q	**4 to < 24 months**	**6.45×10^{-02}**	**1.66×10^{-09}**	**1.47×10^{-02}**	**2.20×10^{-02}**	**1.70×10^{-04}**	**1.90×10^{00}**	**2.20×10^{00}**	**1.30×10^{-01}**	**1.80×10^{-02}**	**7.66×10^{-02}**	**1.18×10^{00}**	**2.90×10^{00}**	**2.36×10^{-02}**	**7.56×10^{00}**	**6.30×10^{-02}**
		0.5 to 1 year	3.50×10^{-04}	4.00×10^{-10}	4.50×10^{-04}	2.37×10^{-03}	2.25×10^{-04}	5.36×10^{-02}	8.62×10^{-02}	1.13×10^{-02}	2.65×10^{-01}	1.39×10^{-05}	6.94×10^{-01}	8.15×10^{-02}	8.00E-11	3.34×10^{-01}	1.43×10^{-02}
		1 to 2 years	1.10×10^{-03}	1.26×10^{-09}	1.42×10^{-03}	7.46×10^{-03}	7.09×10^{-04}	1.69×10^{-01}	2.72×10^{-01}	3.57×10^{-02}	8.34×10^{-01}	4.38×10^{-05}	2.19×10^{00}	2.57×10^{-01}	2.52×10^{-10}	1.05×10^{00}	4.50×10^{-02}
Rice cereal	R	**4 to < 24 months**	**1.45×10^{-03}**	**1.66×10^{-09}**	**1.87×10^{-03}**	**9.83×10^{-03}**	**9.35×10^{-04}**	**2.23×10^{-01}**	**3.58×10^{-01}**	**4.71×10^{-02}**	**1.10×10^{00}**	**5.77×10^{-05}**	**2.88×10^{00}**	**3.38×10^{-01}**	**3.32×10^{-10}**	**1.38×10^{00}**	**5.93×10^{-02}**

Table S5 – Estimated Hazard Quotient (HQ) associated with exposure to iAs in different proportions with the results of HQ above 1 highlighted.

Infant cereal	HQ	
	iAs (52%)	iAs (100%)
Corn cereal (A)	5.47×10^{-02}	1.05×10^{-01}
Oatmeal (B)	1.44×10^{-01}	2.77×10^{-01}
Oatmeal (C)	7.24×10^{-02}	1.39×10^{-01}
Multi-grain cereal (D)	1.48×10^{-01}	2.85×10^{-01}
Rice and oat cereal (E)	3.03×10^{-01}	5.83×10^{-01}
Rice and oat cereal (F)	1.41×10^{00}	2.72×10^{00}
Rice cereal and fruits (G)	1.05×10^{00}	2.01×10^{00}
Rice cereal and maize starch (H)	2.18×10^{-01}	4.19×10^{-01}
Rice cereal and maize starch (I)	1.96×10^{-01}	3.77×10^{-01}
Rice cereal (J)	1.31×10^{00}	2.51×10^{00}
Rice cereal (K)	1.31×10^{00}	2.52×10^{00}
Rice cereal (L)	1.45×10^{00}	2.78×10^{00}
Rice cereal (M)	1.68×10^{00}	3.24×10^{00}
Rice cereal (N)	1.18×10^{00}	2.27×10^{00}
Rice cereal (O)	1.93×10^{00}	3.72×10^{00}
Rice cereal (P)	9.98×10^{-01}	1.92×10^{00}
Rice cereal (Q)	1.51×10^{00}	2.90×10^{00}
Rice cereal (R)	1.76×10^{-01}	3.38×10^{-01}

5.3. MANUSCRITO III

Probabilistic risk assessment from exposure to essential and non-essential elements in rice from Brazil.

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Abstract

Rice, a staple food for half of the world population, has been reported to represent risks to human health due the concentration of hazard elements. Most of the studies evaluating the risks to human health from rice consumption are focused only on the exposure to inorganic arsenic. Thus, the objective of this study is to assess the cancer and non-cancer risk of exposure to toxic and essential elements present in rice from Brazil, excluding inorganic arsenic. The incremental lifetime cancer risk (ILCR), Hazard Quotient (HQ) and Hazard Index were calculated in a probabilistic framework, with Monte Carlo simulation. The elements included in this assessment were Al, B, Ba, Cd, Co, Cr, Cu, Mn, Ni, Pb, Se, Sr and Zn for non-carcinogenic effects, and Pb for the cancer evaluation. The mean ILCR was 2.50×10^{-8}, and the 95th percentile 3.86×10^{-8}, both considered low. The HQ and HI were below 1 for all the elements, suggesting that health effects from this exposure are unlikely. Although the risks related to Pb were found to be tolerable in this risk assessment, no dose of Pb is currently considered safe, and efforts to interrupt any source of exposure, including diet, could bring benefits to public health.

Keywords:

Rice consumption; hazard quotient; cancer risk; toxic elements; lead; food safety

1. Introduction

Rice, a staple food for half of the world population, has been reported to represent risks to human health due the concentration of hazard elements (Fu et al., 2015; Gross & Zhao, 2014; Ma et al., 2017).

Similar to other cereals, rice have this feature of storing elements absorbed from soil and water used for irrigation. The sources can be natural or anthropogenic, and environmental conditions and soil properties (such as pH and soil organic matter) influence the accumulation of certain elements in rice, like As, Cd, Cr and Pb (Liu et al., 2015; Dittmar et al., 2010).

Many studies focus on arsenic concentrations, which the risks have been described in different countries (H. L. Chen et al., 2016; Menon et al., 2020; U.S. FDA, 2016). In addition to arsenic, some studies have evaluated the presence of other elements in rice, such as Al, Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, Se, Va and Zn in rice from different locations. Some of these studies have reported risks to human health (Sharafi et al., 2019; Chen et al., 2018; Giri and Singh, 2017; Praveena and Omar, 2017; Fu et al., 2015). Some of the mentioned elements are toxic, and even a small dose can represent risks to human health. Pb and Cd are on the list of 10 chemicals of major public health concern proposed by the World Health Organization (WHO) (WHO, 2010).

On the other hand, some elements are essential to human health but only in small doses. Elevated doses of essential elements, such as Co, Cu, Mn, Se and Zn, might cause adverse health effects, and non-tolerable risks have been reported (Zoroddu et al., 2019; Keshavarzi et al., 2015).

Quantitative risk assessments have been highlighted by the Food and Agriculture Organization of the United Nations (FAO-UN), as an important tool to assist in risk management and to support decision-making in public health (FAO, 2015).

In Brazil, rice is largely consumed, usually two times per day, with an average ingestion rate for adults of 140.9 g/day (IBGE, 2020). However, there are few studies about the health risks from rice ingestion, and most of them focuses only on arsenic. In this scenario, the objective of this research is to evaluate the cancer and non-cancer risks of a lifetime exposure to essential and non-essential elements present in rice produced in Brazil.

2. Method

2.1. Concentration of essential and non-essential elements in rice

The data related to the concentrations of 20 essential and non-essential elements in brown (husked) rice (Al, B, Ba, Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Ni, Na, P, Pb, Se, Sr, and Zn) were originally reported by Batista et al. (2015). The determination of the essential and non-essential elements in the 69 samples of brown rice was carried out by an inductively coupled plasma mass spectrometer (ICP-MS). That study which we had access is one of the few studies on concentration of the referred elements in rice from Brazil, with samples of rice collected mostly in the main rice-producing region of Brazil, the south of the country, directly from farms where they were cultivated.

For this risk assessment, only the elements with a described slope factor and reference dose were considered.

2.2. Average daily dose, carcinogenic risk, and hazard quotient

As the exposure varies with age, the average daily dose (ADD) was estimated for each age group assuming that exposure to elements present in rice occurred over the lifetime, as follows (U.S. EPA, 1989):

$$ADD_j = \frac{[C \times IRj \times EDj \times EFj]}{[BWj \times AT]} \qquad (1)$$

so that ADD_j is the average daily dose (mg/kg-day) for the age group j for each element, C is the element concentration in rice (mg/g), and IR_j is the ingestion rate (g/day) for the age group *j*. ED_j is the exposure duration (years), and EF_j is the exposure frequency (312.85 days/year, considering a exposure of 6 days/week) both for the age group j; BW_j is the body weight for the age group j, AT is the average time (years), which is the ED_j x 365 days.

The cancer risk was estimated for each age group and each carcinogenic element present in rice, by multiplying the ADDj by the slope factor (SF) of the respective element. By the weighted sum of each estimated cancer risk for each age group, we obtained the incremental lifetime cancer risk (ILCR), according to the equation (USEPA, 2005):

$$ILCR = \sum_{j=1,n} (ADDj \times SF) \times \frac{ED_j}{LT}) \qquad (2)$$

where LT is the lifetime (70 years), and n is the number of age intervals.

The potential non-cancer risk of an individual element and for a specific age group is expressed as the fractional hazard quotient, by the ratio of the ADDj with the reference dose (RfD) of each non-carcinogenic substance. Hazard Quotient (HQ) for each element was obtained by summing each fractional hazard quotient, weighted by the EDj and AT, contemplating a lifetime of exposure:

$$HQ = \sum_{j=1,n} (\frac{ADD_j}{RfD}) \times \frac{ED_j}{AT} \qquad (3)$$

Considering the exposure to a mixture of chemicals which have the same major effects, the calculated HQs were summed, resulting in the Hazard Index (HI) (USEPA, 2000b) U.S. EPA, 1989).

2.3. Rice consumption and exposure frequency

We assumed the ingestion rates of white (polished) rice, since in Brazil there is not data available specifically for brown rice. The rice consumption for each age group, which includes only rice grain, was acquired from different sources, also presented in table 1:

- 4 months to 1 year and 5 to 10 years— we assumed the rice daily ingestion recommended by the São Paulo Municipal Department of Education for consumption in schools and daycare centers (São Paulo, 2011a, 2011b). We estimated the actual rice consumption to be 39.8% less than the proposed by the guideline, based on comparison to the actual consumption for children 1 to 5 years of age (as shown below). Differently from earlier age groups, from 6 to 10 years of age students have a part-time school period, receiving only one meal at school (lunch or dinner). Thus, daily rice consumption for that age group was estimated to be double than the recommended by the guideline, assuming that people in Brazil have two meals a day containing rice.
- 1 to 5 years— we had access to the complete data set of rice consumption of 64 children at home and at two daycare centers in the city of São Paulo which was evaluated by Leroux et al. (2018). They analyzed the 24-h duplicate diet. We followed nutrition guidelines to convert household measures (*e.g.*, tablespoons) to grams (Bompem et al., 2012; Tomita & Cardoso, 2000).
- 10 to 70 years—data were acquired from a national study in which the interviewed population reported the consumption of rice in the last 48 h (IBGE, 2020).

2.4. Body weight

Body weight was estimated for each age group by the weighted average of the male and female population, relative to the total interviewed population of a major national study (IBGE, 2010).

2.5. Data analysis and probabilistic assessment

The statistical analysis was performed with R software, version 3.5.0, and R studio, version 1.1.453 (The R Foundation for Statistical Computing, Vienna, Austria). We fitted the distribution of the elements concentration data set using the fitdistrplus package. The distribution (normal, lognormal and exponential) with the lowest Akaike information criterion value was selected.

The ILCR, HQ and HI estimations were implemented in a probabilistic framework, with the open-source software YASAIw, from the State of Washington Department of Ecology (Pelletier & Box, 2009). The Monte Carlo simulations, with 10,000 iterations, were performed using distributions for the concentration of the selected elements in rice, with a confidence interval of 95%.

Table 1 presents the summary of the parameters adopted for the risk assessment.Table 1 - Parameters adopted for assessing the risk of exposure to essential and non-essential elements present in rice.

Age (years)	Body weight (kg)*	Rice ingestion (g/day of row rice)**	Exposure duration (years)
< 1	7.82	9.0	0.75***
1	11.19	54.9	1.00
2	13.70	54.0	1.00
3	15.71	60.6	1.00
4	17.80	66.7	1.00
5	19.77	58.2	1.00
6	22.17	60.2	1.00
7	24.98	60.2	1.00
8	27.70	60.2	1.00
9	31.66	60.2	1.00
10	33.82	47.9	1.00
11	38.11	47.9	1.00
12	43.06	47.9	1.00
13	47.66	47.9	1.00
14	51.21	47.9	1.00
15	54.87	47.9	1.00
16	56.82	47.9	1.00
17	58.79	47.9	1.00
18	60.38	47.9	1.00
19	61.18	49.1	1.00
20 to <25	63.77	49.1	5.00
25 to <30	66.70	49.1	5.00
30 to <35	67.95	49.1	5.00
35 to <45	68.94	49.1	10.00
45 to <55	69.54	49.1	10.00
55 to <65	68.93	45.0	10.00
65 to <70	66.52	40.9	10.00

*IBGE (2010);
*** IBGE (2020); Leroux et al., (2018); São Paulo, 2011a; São Paulo, 2011b.
**According to the São Paulo Municipal Department of Education guidelines for food consumption at daycare centers, infants should not be fed rice until 4 months of age (São Paulo, 2011a)

3. Results and discussion

3.1. Selection of essential and non-essential elements for the risk assessment and its concentration in infant cereal

Only four out of 21 elements are assessed by the International Agency for Research on Cancer (IARC): Cd, Al and Ni are carcinogenic to humans (group 1), Pb is probably carcinogenic to humans (group 2A), and Se and Cr are not classifiable as to its carcinogenicity to humans (group 3) (IARC, 2020). A cancer slope factor is available only for Pb (8.5 $x10^{-3}$ $mg/kg\text{-}day^{-1}$)(OEHHA, 2020). The Reference Dose (RfD) for non-cancer effects and its respective target systems are available for 13 elements, as showed in table 2.

Table 2 – Essential and non-essential elements and its reference dose for non-cancer health effects adopted for the risk assessment.

	RfD (mg/kg -day)	System	Reference
Aluminum	1	Neurological	(ATSDR, 2008)
Boron	2×10^{-1}	Gastrointestinal	(USEPA, 2004)
Barium	2×10^{-1}	Urinary	(USEPA, 2005a)
Cadmium	$1.10 \times ^{-5}$*, 1×10^{-3}	Urinary	(OEHHA, 2005)* (USEPA, 1987a)
Cobalt	1×10^{-2}	Hematological	(ATSDR, 2004a)
Chromium	1	Other	(USEPA, 1998)
Cupper	1×10^{-2}	Gastrointestinal	(ATSDR, 2004b)
Manganese	3×10^{-2}*, 1.4×10^{-1}	Nervous	(OEHHA, 2006)* (USEPA, 1995)
Nickel	1.1×10^{-2}*, 2×10^{-2}	Other	(OEHHA, 2005)* (USEPA, 1987b)
Lead	3.5×10^{-3}**	Neurological	(Joint FAO/WHO, 2011).
Selenium	5×10^{-3}	Nervous, hematologic, and dermal	(USEPA, 1991)
Strontium	6×10^{-1}	Musculoskeletal	(USEPA, 1992)
Zinc	3×10^{-1}	Immune, and hematologic	(USEPA, 2005b)

*Child specific Rfd; ** RfD calculated according to the withdrawn FAO's provisional tolerable weekly intake (PTWI) (Joint FAO/WHO, 2011).

The elements Cr and Ni were classified as "other" regarding its human target system. The data about chromium III and insoluble salts has high level of uncertainty about the non-cancer health effects. The health effects reported from animal studies are associated with high dose of Cr (III) and reductions in the absolute weights of the livers and spleens. Very limited data suggest that Cr(III) can cause respiratory effects on humans (USEPA, 1998). For nickel, the studies that based the development of the oral RfD found decrease in body and organs weights (USEPA, 1987b).

The distribution lognormal had a better fit in the data of concentration of elements in rice. The parameters of the distribution are described in table 3, as the mean, standard deviation, and confidence interval. The number of samples were 69, except for Co (28) and Zn (68).

Table 3 – Parameters of the lognormal distributions of the concentration of substances in rice

Element	Concentration Mean; SD (ng g^{-1})	95% CI* (ng g^{-1})	Lognormal parameters (μ; δ)
Al	793.9; 1268.7	489.1 – 1098.7	2.4; 7.1
B	2,091.0; 4,171.5	1,088.9 – 3,093.1	7.1; 0.8
Ba	864.6; 529.0	737.5 – 991.7	6.6; 0.6
Cd	11.7; 6.7	10.1 – 13.3	2.4; 0.5
Co	74.6; 88.0	40.5 – 108.7	3.8; 0.9
Cr	28.9; 24.49	23.0 – 34.8	3.2; 0.6
Cu	3,410.3; 840.4	3,208.4 – 3,612.2	8.1; 0.2
Mn	3,3682.3; 1,2209.1	3,0749.3 – 3,6615.2	10.4; 0.4
Ni	313.5; 145.8	278.4 – 348.5	5.6; 0.5
Pb	43.7; 49.7	31.8 – 55.7	3.3; 1.0
Se	42.2; 10.5	39.7 – 44.7	3.7; 0.2
Sr	461.0; 98.2	437.4 – 484.5	6.1; 0.2
Zn	2,3516.3; 5,702.7	2,2135.9 – 24896.6	10.0; 0.2

Source: (Batista, 2015). *95% CI = 95% confidence intervals for estimated means.

The literature reports a maximum contaminant level (MCL) only for Cd and Pb. For Cd in rice, the MCL is 400 ng g^{-1} (Joint FAO/WHO, 2018), or 200 ng g^{-1} (EC, 2014). None of the samples used in this study have a concentration of Cd above any of the MCLs. The same agencies have proposed a MCL for Pb in cereals, not specifically rice, of 200 ng g^{-1} (Joint FAO/WHO, 2015; EC, 2015). In this case, we would have 3 samples of rice (4.4%) with concentrations of Pb above the MCL.

Nacano et al. (2014) evaluated the presence of some toxic elements in food available in two schools of the city of Ribeirao Preto (Sao Paulo, Brazil). The concentration of Cd in rice (n=121) was 11.4 ± 5.6 ng g^{-1}, similar to ours, and Pb was 1.1 ± 1.7 ng g^{-1}, significantly lower than the mean value of the samples we are using (Batista, 2015).

Al-Saleh and Abduljabbar (2017) assessed the concentration of Pb and Cd in 61 samples of rice from India, Thailand, United States of America, Italy, Indonesia, Iraq, Pakistan, Australia and Spain. One sample contained lead above the MCL proposed by the FAO. Differently, Giri and Singh (2017) collected 14 samples of rice in a paddy field near to a mining area, in India. The concentrations of Ni, Pb and Zn in a few samples exceeded the limits of Indian standard for food. The highest concentrations were associated to the proximity to mining areas.

Xue et al. (2017) found a mean concentration of Cd in samples of rice grown near to a mining area to be 1,100 ± 2,100.0 ng g^{-1}, and Pb 5,240.0 14,500.0 ng g^{-1}, both above FAO's MCL. The high concentrations and expressive variability, much higher than values of this study, were attributed to external inputs from human activities.

3.2. Cancer risk, Hazard Quotient and Hazard Index of exposure to essential and non-essential elements in rice

Table 4 presents the dose (mean and 95%UCI), incremental cancer risks by age group and the ILCR (mean and 95%UCI) of exposure to Pb in rice. Table S1 (in the supplementary material) shows the results of the non-cancer risk assessment for each element. The results of the fractional HI calculations are given in table S2 (in the supplementary material) and the HI for a lifetime are given in table 5.

Table 4 – Estimated dose (ADD), incremental cancer risks and incremental lifetime cancer risk (ILCR) associated with exposure to Pb present in rice.

Age group	ADD		Incremental cancer risks	
	Mean	95%UCI*	Mean	95%UCI
< 1 year	3.28×10^{-06}	5.07×10^{-06}	2.80×10^{-10}	4.32×10^{-10}
1 year	1.39×10^{-05}	2.15×10^{-05}	1.58×10^{-09}	2.45×10^{-09}
2 years	1.12×10^{-05}	1.73×10^{-05}	1.27×10^{-09}	1.97×10^{-09}
3 years	1.10×10^{-05}	1.69×10^{-05}	1.25×10^{-09}	1.93×10^{-09}
4 years	1.06×10^{-05}	1.65×10^{-05}	1.21×10^{-09}	1.87×10^{-09}
5 years	8.37×10^{-06}	1.29×10^{-05}	9.51×10^{-10}	1.47×10^{-09}
6 years	7.72×10^{-06}	1.19×10^{-05}	8.77×10^{-10}	1.36×10^{-09}
7 years	6.85×10^{-06}	1.06×10^{-05}	7.79×10^{-10}	1.20×10^{-09}
8 years	6.18×10^{-06}	9.55×10^{-06}	7.02×10^{-10}	1.09×10^{-09}
9 years	5.40×10^{-06}	8.35×10^{-06}	6.14×10^{-10}	9.50×10^{-10}
10 years	4.03×10^{-06}	6.22×10^{-06}	4.58×10^{-10}	7.08×10^{-10}
11 years	3.57×10^{-06}	5.52×10^{-06}	4.06×10^{-10}	6.28×10^{-10}
12 years	3.16×10^{-06}	4.89×10^{-06}	3.60×10^{-10}	5.56×10^{-10}
13 years	2.86×10^{-06}	4.42×10^{-06}	3.25×10^{-10}	5.02×10^{-10}
14 years	2.66×10^{-06}	4.11×10^{-06}	3.02×10^{-10}	4.67×10^{-10}
15 years	2.48×10^{-06}	3.84×10^{-06}	2.82×10^{-10}	4.36×10^{-10}
16 years	2.40×10^{-06}	3.70×10^{-06}	2.72×10^{-10}	4.21×10^{-10}
17 years	2.32×10^{-06}	3.58×10^{-06}	2.63×10^{-10}	4.07×10^{-10}
18 years	2.25×10^{-06}	3.49×10^{-06}	2.56×10^{-10}	3.96×10^{-10}
19 years	2.28×10^{-06}	3.52×10^{-06}	2.59×10^{-10}	4.01×10^{-10}
20 to < 25 years	2.19×10^{-06}	3.38×10^{-06}	1.24×10^{-09}	1.92×10^{-09}
25 to <30 years	2.05×10^{-06}	3.17×10^{-06}	1.19×10^{-09}	1.84×10^{-09}
30 to <35 years	2.09×10^{-06}	3.23×10^{-06}	1.17×10^{-09}	1.80×10^{-09}
35 to <45 years	2.02×10^{-06}	3.13×10^{-06}	2.30×10^{-09}	3.56×10^{-09}
45 to <55 years	2.01×10^{-06}	3.10×10^{-06}	2.28×10^{-09}	3.53×10^{-09}
55 to <65 years	1.86×10^{-06}	2.87×10^{-06}	2.11×10^{-09}	3.26×10^{-09}
65 to <70 years	1.75×10^{-06}	2.70×10^{-06}	1.99×10^{-09}	3.07×10^{-09}
ILCR	-	-	2.50×10^{-08}	3.86×10^{-08}

*95%UCI: Upper limit of the 95% confident interval

Table 5 – Estimated hazard index (HI) for exposure to essential and non-essential elements in rice by biological system affected.

System	HI	
	Mean	95th percentile
Neurological	8.54×10^{-04}	1.34×10^{-03}
Gastrointestinal	7.56×10^{-04}	7.99×10^{-04}
Urinary	1.12×10^{-01}	1.52×10^{-01}
Hematological	1.03×10^{-03}	1.26×10^{-03}
Nervous	8.58×10^{-04}	9.40×10^{-04}

The ILCR related to Pb is considered low. There is no guideline for an acceptable level of risk due hazard chemicals in food. For comparison, a few authors use the acceptable risk range ($1 \times 10^{-6} – 1 \times 10^{-4}$) proposed by the United States Protection Agency (USEPA, 2000a) for contaminated areas, and the limit of 1×10^{-5} adopted by the WHO for non-threshold substances in drinking water (WHO, 2017). Our ILCR is lower than both guidelines. Similar results were reported by Praveena and Omar (2017) in a risk assessment conducted in Malaysia with 66 samples of different kinds of rice, where the risk attributed to Pb was reported to be lower than 10^{-5}.

Although we cannot quantify, there is a cancer risk from exposure to Cd, Al and Ni present in rice (IARC, 2020). Carcinogens are assumed to be non-threshold substances, because there is no level of exposure to such a chemical that does not pose a probability, even that it is small, of causing a carcinogenic response. Thus, no dose of a non-threshold chemical is free of risk (U.S. EPA, 1989). The presence of more than one carcinogenic substances requires the summing of its respective cancer risks (U.S. EPA, 1989), thus the actual ILCR in the scenario we proposes in this research is higher than 2.5×10^{-8} .

The HQ is below 1 for all elements, which means that health effects are not likely. Cd was the element with the highest mean HQ (1.11×10^{-1}), and Al the lowest (2.04×10^{-6}). Similar results were reported by Praveena and Omar (2017), who assessed the non-carcer risk related to Cr, Cu, Cd, Fe, Zn, Al, Co, Pb in rice in Malaysia (n = 66), all HQs below 1. Chen et al. (2018) found an HQ below 1 for 32 samples of rice grown in a contaminated area of China. They evaluated Cd, Cr, Cu, Ni, Pb and Zn. Similarly, Giri and Singh (2017) found an HQ below 1 for Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, Se, V and Zn. The 14 samples of rice were collected from different points of a contaminated area, in India.

The HI found was below unit for all major effects, indicating that consuming rice might be safe from the point of view of non-carcinogenic effects for the elements studied. The highest mean HI was related to urinary system (1.12×10^{-1}), corresponding to the exposure to Ba and Cd. We highlight that we followed the EPA’s guidance for chemicals mixtures, which determines that the Hazard Index method is specifically recommended only for groups of toxicologically similar chemicals that all have dose-response data, or at least have similarity of target organs

(USEPA, 2000b). If we have summed all the HQ regardless the target organ or system, as we can see in many studies, the result would be 1.15 x 10^{-1}, still below 1.

Although our results point to a not significative cancer and non-cancer risk, the exposure to Pb is always undesirable. Currently, there is no level of Pb ingestion considered safe (JECFA, 2011).

Lead exposure is a worldwide issue and can vary according to countries (Obeng-Gyasi, 2019). The ingestion of contaminated food and drinking water can be important sources of exposure. All categories of food are known to contain a certain level of lead, due mainly to remaining soil on the food, atmospheric deposition, processing, and packaging. The ingestion of contaminated soil or dust, and lead-based paint are also significative (ATSDR, 2020; JECFA, 2011). The exposure is not restricted to diet, other currently reported sources of exposure to lead are electronic waste, batteries, glazed ceramics, lead contaminated utensils, cosmetics, traditional medicines, industrial emissions, and toys. Exposure to lead is a matter in both high-income countries and lower- and middle-income countries (Obeng-Gyasi, 2019). Olympio et al (2018), in a cross-sectional study in Sao Paulo (Brazil), found a geographic association between day care centers and the blood lead levels in children. They found evidence that the vehicles flow and red lead in household gates was also an important risk factor for lead exposure. In the same city, Silva et al (2018) reported that the blood lead levels of children were associated to the lead levels of day care centers, highlighting tiles and playground equipment as the main source of exposure, due to lead painting. Still in Brazil, Ferreira et al. (2019) conducted a study in the city of Limeira (Sao Paulo), and reported exposure of families to lead at home, due working informally in the productive chain of jewelry.

The health effects resulting from exposure to lead overlap with other common metals. Besides being carcinogenic, lead is known to cause neurotoxicity, which includes cognitive, affective, and physiological damages. Many studies have shown that Pb exposure can cause decreases in intelligence, memory, processing speed, comprehension and reading, visuospatial skills, motor skills and antisocial behavior (Mason et al., 2014; Kelly P.K. Olympio et al., 2010).

Great attention has been paid to early exposure to lead since children are more vulnerable. Many studies have reported attention deficit, difficulty concentrating and learning, decreased motor skills, and increased aggressive behavior (ATSDR, 2020; Zhang et al., 2013; WHO, 2010; Olympio et al., 2009).

Delgado et al. (2018), in a study with 85,178 children with average age 2.6 years identified an association between lead exposure and intellectual and educational outcomes. They concluded that there is a necessity of prevention and surveillance efforts to decrease the negative impacts of lead on society.

Fetal exposure to lead is also a public health issue. Zajac et al. (2020), in their probabilistic approach, found that pregnant women living near to a contaminated area had blood lead levels that put their fetus at risk for neurologic damage and other sequelae. In a prospective birth cohort in China, Cheng et al.(2017) reported association between risk of preterm births with urinary lead levels.

Our results would probably be different if we have included in this risk assessment rice products. Nacano et al. (2014) identified a concentration of Cd of 18.5 ± 13.7, and Pb of 1.7 ± 1.9 in 17 samples of rice porridge. Other rice products, for instance rice cereal, crackers, and others, should be considered for a more comprehensive risk assessment due rice consumption.

Having samples collected in different periods of the year could reveal a different result, as reported by Nacano et al. (2014). They identified in a study in different schools that the concentration of Cd and Pb in rice varied significantly according to location and period of the year, suggesting the environment play an important role in the concentration of these metal in rice, and consequently the risk.

In this study the synergistic chemical interaction was not considered, thus is possible that the results are underestimated (U.S. EPA, 1989).

4. Conclusion

In this risk assessment we evaluated if essential and non-essential elements can represent risks to human health by rice consumption. Our results suggest that the incremental lifetime cancer risk is low and non-cancer risk is tolerable for the essential and non-essential elements assessed, even with the typically elevated rice intake in Brazil.

Although the cancer risk for exposure to Pb in rice is low, the intake of this element, even in small doses, is not considered safe and the environmental exposure to lead has been considered a relevant issue for public health, particularly for infants and children. Thus, efforts to cease all possible sources of exposure could bring benefits to public health.

The presence of samples of rice with Pb concentrations above the MCL could indicate a necessity to further investigations. A study using more samples of rice and collected in different periods of the year and distinct locations, could lead to a different result of risk. The actual risk is probably higher, since we assessed only rice grains, not including rice products. Also, the absence of cancer slope factor for some carcinogenic elements occasioned in underestimated risks results.

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Supplementary material

Table S1– Fractional Hazard Quotient (HQ) and lifetime HQ of exposure to essential and non-essential elements present in infant cereal

Age	Al		B		Ba		Cd		Co		Cr		Cu		Mn		Ni		Pb		Se		Sr		Zn	
	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile
< 1	2.4×10^{-08}	9.5×10^{-08}	3.8×10^{-07}	4.5×10^{-07}	3.5×10^{-07}	4.1×10^{-07}	2.5×10^{-03}	3.4×10^{-03}	4.1×10^{-06}	5.9×10^{-06}	3.4×10^{-08}	4.5×10^{-08}	8.6×10^{-06}	9.1×10^{-06}	3.7×10^{-06}	3.9×10^{-06}	5.5×10^{-06}	6.2×10^{-06}	1.0×10^{-05}	1.6×10^{-05}	7.9×10^{-06}	8.7×10^{-06}	1.1×10^{-07}	1.1×10^{-07}	3.6×10^{-07}	3.7×10^{-07}
1	1.4×10^{-07}	5.4×10^{-07}	2.1×10^{-06}	2.5×10^{-06}	2.0×10^{-06}	2.3×10^{-06}	1.4×10^{-02}	1.9×10^{-02}	2.3×10^{-05}	3.3×10^{-05}	1.9×10^{-07}	2.5×10^{-07}	4.9×10^{-05}	5.1×10^{-05}	2.1×10^{-05}	2.2×10^{-05}	3.1×10^{-05}	3.5×10^{-05}	5.7×10^{-05}	9.0×10^{-05}	4.5×10^{-05}	4.9×10^{-05}	6.1×10^{-07}	6.5×10^{-07}	2.0×10^{-06}	2.1×10^{-06}
2	1.1×10^{-07}	4.3×10^{-07}	1.7×10^{-06}	2.0×10^{-06}	1.6×10^{-06}	1.8×10^{-06}	1.1×10^{-02}	1.5×10^{-02}	1.8×10^{-05}	2.7×10^{-05}	1.5×10^{-07}	2.0×10^{-07}	3.9×10^{-05}	4.1×10^{-05}	1.7×10^{-05}	1.8×10^{-05}	2.5×10^{-05}	2.8×10^{-05}	4.6×10^{-05}	7.2×10^{-05}	3.6×10^{-05}	4.0×10^{-05}	4.9×10^{-07}	5.2×10^{-07}	1.6×10^{-06}	1.7×10^{-06}
3	1.1×10^{-07}	4.2×10^{-07}	1.7×10^{-06}	2.0×10^{-06}	1.6×10^{-06}	1.8×10^{-06}	1.1×10^{-02}	1.5×10^{-02}	1.8×10^{-05}	2.6×10^{-05}	1.5×10^{-07}	2.0×10^{-07}	3.8×10^{-05}	4.0×10^{-05}	1.6×10^{-05}	1.7×10^{-05}	2.4×10^{-05}	2.8×10^{-05}	4.5×10^{-05}	7.1×10^{-05}	3.5×10^{-05}	3.9×10^{-05}	4.8×10^{-07}	5.1×10^{-07}	1.6×10^{-06}	1.6×10^{-06}
4	1.1×10^{-07}	4.1×10^{-07}	1.6×10^{-06}	1.9×10^{-06}	1.5×10^{-06}	1.8×10^{-06}	1.1×10^{-02}	1.5×10^{-02}	1.8×10^{-05}	2.5×10^{-05}	1.5×10^{-07}	1.9×10^{-07}	3.7×10^{-05}	3.9×10^{-05}	1.6×10^{-05}	1.7×10^{-05}	2.4×10^{-05}	2.7×10^{-05}	4.4×10^{-05}	6.9×10^{-05}	3.4×10^{-05}	3.8×10^{-05}	4.7×10^{-07}	4.9×10^{-07}	1.5×10^{-06}	1.6×10^{-06}
5	8.3×10^{-08}	3.2×10^{-07}	1.3×10^{-06}	1.5×10^{-06}	1.2×10^{-06}	1.4×10^{-06}	8.5×10^{-03}	1.1×10^{-02}	1.4×10^{-05}	2.0×10^{-05}	1.1×10^{-07}	1.5×10^{-07}	2.9×10^{-05}	3.1×10^{-05}	1.2×10^{-05}	1.3×10^{-05}	1.9×10^{-05}	2.1×10^{-05}	3.4×10^{-05}	5.4×10^{-05}	2.7×10^{-05}	3.0×10^{-05}	3.7×10^{-07}	3.9×10^{-07}	1.2×10^{-06}	1.3×10^{-06}
6	7.6×10^{-08}	3.0×10^{-07}	1.2×10^{-06}	1.4×10^{-06}	1.1×10^{-06}	1.3×10^{-06}	7.8×10^{-03}	1.1×10^{-02}	1.3×10^{-05}	1.8×10^{-05}	1.1×10^{-07}	1.4×10^{-07}	2.7×10^{-05}	2.8×10^{-05}	1.2×10^{-05}	1.2×10^{-05}	1.7×10^{-05}	2.0×10^{-05}	3.2×10^{-05}	5.0×10^{-05}	2.5×10^{-05}	2.7×10^{-05}	3.4×10^{-07}	3.6×10^{-07}	1.1×10^{-06}	1.2×10^{-06}
7	6.8×10^{-08}	2.6×10^{-07}	1.1×10^{-06}	1.2×10^{-06}	9.7×10^{-07}	1.1×10^{-06}	6.9×10^{-03}	9.4×10^{-03}	1.1×10^{-05}	1.6×10^{-05}	9.4×10^{-08}	1.2×10^{-07}	2.4×10^{-05}	2.5×10^{-05}	1.0×10^{-05}	1.1×10^{-05}	1.5×10^{-05}	1.7×10^{-05}	2.8×10^{-05}	4.4×10^{-05}	2.2×10^{-05}	2.4×10^{-05}	3.0×10^{-07}	3.2×10^{-07}	9.9×10^{-07}	1.0×10^{-06}
8	6.1×10^{-08}	2.4×10^{-07}	9.5×10^{-07}	1.1×10^{-06}	8.8×10^{-07}	1.0×10^{-06}	6.3×10^{-03}	8.5×10^{-03}	1.0×10^{-05}	1.5×10^{-05}	8.4×10^{-08}	1.1×10^{-07}	2.2×10^{-05}	2.3×10^{-05}	9.2×10^{-06}	9.8×10^{-06}	1.4×10^{-05}	1.6×10^{-05}	2.5×10^{-05}	4.0×10^{-05}	2.0×10^{-05}	2.2×10^{-05}	2.7×10^{-07}	2.9×10^{-07}	8.9×10^{-07}	9.3×10^{-07}
9	5.4×10^{-08}	2.1×10^{-07}	8.3×10^{-07}	9.8×10^{-07}	7.7×10^{-07}	8.9×10^{-07}	5.5×10^{-03}	7.4×10^{-03}	8.9×10^{-06}	1.3×10^{-05}	7.4×10^{-08}	9.8×10^{-08}	1.9×10^{-05}	2.0×10^{-05}	8.1×10^{-06}	8.5×10^{-06}	1.2×10^{-05}	1.4×10^{-05}	2.2×10^{-05}	3.5×10^{-05}	1.7×10^{-05}	1.9×10^{-05}	2.4×10^{-07}	2.5×10^{-07}	7.8×10^{-07}	8.1×10^{-07}
10	4.0×10^{-08}	1.6×10^{-07}	6.2×10^{-07}	7.3×10^{-07}	5.7×10^{-07}	6.6×10^{-07}	4.1×10^{-03}	5.5×10^{-03}	6.6×10^{-06}	9.6×10^{-06}	5.5×10^{-08}	7.3×10^{-08}	1.4×10^{-05}	1.5×10^{-05}	6.0×10^{-06}	6.4×10^{-06}	8.9×10^{-06}	1.0×10^{-05}	1.7×10^{-05}	2.6×10^{-05}	1.3×10^{-05}	1.4×10^{-05}	1.8×10^{-07}	1.9×10^{-07}	5.8×10^{-07}	6.1×10^{-07}
11	3.5×10^{-08}	1.4×10^{-07}	5.5×10^{-07}	6.5×10^{-07}	5.1×10^{-07}	5.9×10^{-07}	3.6×10^{-03}	4.9×10^{-03}	5.9×10^{-06}	8.5×10^{-06}	4.9×10^{-08}	6.5×10^{-08}	1.3×10^{-05}	1.3×10^{-05}	5.3×10^{-06}	5.6×10^{-06}	7.9×10^{-06}	9.0×10^{-06}	1.5×10^{-05}	2.3×10^{-05}	1.1×10^{-05}	1.3×10^{-05}	1.6×10^{-07}	1.7×10^{-07}	5.2×10^{-07}	5.4×10^{-07}
12	3.1×10^{-08}	1.2×10^{-07}	4.9×10^{-07}	5.8×10^{-07}	4.5×10^{-07}	5.2×10^{-07}	3.2×10^{-03}	4.3×10^{-03}	5.2×10^{-06}	7.5×10^{-06}	4.3×10^{-08}	5.7×10^{-08}	1.1×10^{-05}	1.2×10^{-05}	4.7×10^{-06}	5.0×10^{-06}	7.0×10^{-06}	8.0×10^{-06}	1.3×10^{-05}	2.0×10^{-05}	1.0×10^{-05}	1.1×10^{-05}	1.4×10^{-07}	1.5×10^{-07}	4.6×10^{-07}	4.8×10^{-07}
13	2.8×10^{-08}	1.1×10^{-07}	4.4×10^{-07}	5.2×10^{-07}	4.1×10^{-07}	4.7×10^{-07}	2.9×10^{-03}	3.9×10^{-03}	4.7×10^{-06}	6.8×10^{-06}	3.9×10^{-08}	5.2×10^{-08}	1.0×10^{-05}	1.1×10^{-05}	4.3×10^{-06}	4.5×10^{-06}	6.3×10^{-06}	7.2×10^{-06}	1.2×10^{-05}	1.8×10^{-05}	9.2×10^{-06}	1.0×10^{-05}	1.3×10^{-07}	1.3×10^{-07}	4.1×10^{-07}	4.3×10^{-07}
14	2.6×10^{-08}	1.0×10^{-07}	4.1×10^{-07}	4.8×10^{-07}	3.8×10^{-07}	4.4×10^{-07}	2.7×10^{-03}	3.6×10^{-03}	4.4×10^{-06}	6.3×10^{-06}	3.6×10^{-08}	4.8×10^{-08}	9.3×10^{-06}	9.8×10^{-06}	4.0×10^{-06}	4.2×10^{-06}	5.9×10^{-06}	6.7×10^{-06}	1.1×10^{-05}	1.7×10^{-05}	8.5×10^{-06}	9.4×10^{-06}	1.2×10^{-07}	1.2×10^{-07}	3.8×10^{-07}	4.0×10^{-07}
15	2.5×10^{-08}	9.6×10^{-08}	3.8×10^{-07}	4.5×10^{-07}	3.5×10^{-07}	4.1×10^{-07}	2.5×10^{-03}	3.4×10^{-03}	4.1×10^{-06}	5.9×10^{-06}	3.4×10^{-08}	4.5×10^{-08}	8.7×10^{-06}	9.1×10^{-06}	3.7×10^{-06}	3.9×10^{-06}	5.5×10^{-06}	6.3×10^{-06}	1.0×10^{-05}	1.6×10^{-05}	8.0×10^{-06}	8.8×10^{-06}	1.1×10^{-07}	1.2×10^{-07}	3.6×10^{-07}	3.7×10^{-07}
16	2.4×10^{-08}	9.3×10^{-08}	3.7×10^{-07}	4.4×10^{-07}	3.4×10^{-07}	4.0×10^{-07}	2.4×10^{-03}	3.3×10^{-03}	4.0×10^{-06}	5.7×10^{-06}	3.3×10^{-08}	4.3×10^{-08}	8.4×10^{-06}	8.8×10^{-06}	3.6×10^{-06}	3.8×10^{-06}	5.3×10^{-06}	6.1×10^{-06}	9.9×10^{-06}	1.5×10^{-05}	7.7×10^{-06}	8.5×10^{-06}	1.1×10^{-07}	1.1×10^{-07}	3.5×10^{-07}	3.6×10^{-07}
17	2.3×10^{-08}	8.9×10^{-08}	3.6×10^{-07}	4.2×10^{-07}	3.3×10^{-07}	3.8×10^{-07}	2.3×10^{-03}	3.2×10^{-03}	3.8×10^{-06}	5.5×10^{-06}	3.2×10^{-08}	4.2×10^{-08}	8.1×10^{-06}	8.5×10^{-06}	3.5×10^{-06}	3.7×10^{-06}	5.1×10^{-06}	5.9×10^{-06}	9.6×10^{-06}	1.5×10^{-05}	7.4×10^{-06}	8.2×10^{-06}	1.0×10^{-07}	1.1×10^{-07}	3.4×10^{-07}	3.5×10^{-07}
18	2.2×10^{-08}	8.7×10^{-08}	3.5×10^{-07}	4.1×10^{-07}	3.2×10^{-07}	3.7×10^{-07}	2.3×10^{-03}	3.1×10^{-03}	3.7×10^{-06}	5.4×10^{-06}	3.1×10^{-08}	4.1×10^{-08}	7.9×10^{-06}	8.3×10^{-06}	3.4×10^{-06}	3.6×10^{-06}	5.0×10^{-06}	5.7×10^{-06}	9.3×10^{-06}	1.5×10^{-05}	7.2×10^{-06}	8.0×10^{-06}	9.9×10^{-08}	1.0×10^{-07}	3.3×10^{-07}	3.4×10^{-07}
19	2.3×10^{-08}	8.8×10^{-08}	3.5×10^{-07}	4.1×10^{-07}	3.2×10^{-07}	3.8×10^{-07}	2.3×10^{-05}	3.1×10^{-05}	3.8×10^{-06}	5.4×10^{-06}	3.1×10^{-08}	4.1×10^{-08}	8.0×10^{-06}	8.4×10^{-06}	7.3×10^{-07}	7.7×10^{-07}	2.8×10^{-06}	3.2×10^{-06}	9.4×10^{-06}	1.5×10^{-05}	7.3×10^{-06}	8.1×10^{-06}	1.0×10^{-07}	1.1×10^{-07}	3.3×10^{-07}	3.4×10^{-07}
20 to <25	1.1×10^{-07}	4.2×10^{-07}	1.7×10^{-06}	2.0×10^{-06}	1.6×10^{-06}	1.8×10^{-06}	1.1×10^{-04}	1.5×10^{-04}	1.8×10^{-05}	2.6×10^{-05}	1.5×10^{-07}	2.0×10^{-07}	3.8×10^{-05}	4.0×10^{-05}	3.5×10^{-06}	3.7×10^{-06}	1.3×10^{-05}	1.5×10^{-05}	4.5×10^{-05}	7.1×10^{-05}	3.5×10^{-05}	3.9×10^{-05}	4.8×10^{-07}	5.1×10^{-07}	1.6×10^{-06}	1.6×10^{-06}
25 to <30	1.0×10^{-07}	4.0×10^{-07}	1.6×10^{-06}	1.9×10^{-06}	1.5×10^{-06}	1.7×10^{-06}	1.1×10^{-04}	1.4×10^{-04}	1.7×10^{-05}	2.5×10^{-05}	1.4×10^{-07}	1.9×10^{-07}	3.7×10^{-05}	3.9×10^{-05}	3.3×10^{-06}	3.5×10^{-06}	1.3×10^{-05}	1.5×10^{-05}	4.3×10^{-05}	6.8×10^{-05}	3.4×10^{-05}	3.7×10^{-05}	4.6×10^{-07}	4.9×10^{-07}	1.5×10^{-06}	1.6×10^{-06}
30 to <35	1.0×10^{-07}	4.0×10^{-07}	1.6×10^{-06}	1.9×10^{-06}	1.5×10^{-06}	1.7×10^{-06}	1.0×10^{-04}	1.4×10^{-04}	1.7×10^{-05}	2.5×10^{-05}	1.4×10^{-07}	1.9×10^{-07}	3.6×10^{-05}	3.8×10^{-05}	3.3×10^{-06}	3.5×10^{-06}	1.3×10^{-05}	1.4×10^{-05}	4.2×10^{-05}	6.6×10^{-05}	3.3×10^{-05}	3.6×10^{-05}	4.5×10^{-07}	4.8×10^{-07}	1.5×10^{-06}	1.5×10^{-06}
35 to	2.0×10^{-07}	7.8×10^{-07}	3.1×10^{-06}	3.7×10^{-06}	2.9×10^{-06}	3.3×10^{-06}	2.1×10^{-04}	2.8×10^{-04}	3.3×10^{-05}	4.8×10^{-05}	2.8×10^{-07}	3.7×10^{-07}	7.1×10^{-05}	7.5×10^{-05}	6.5×10^{-06}	6.9×10^{-06}	2.5×10^{-05}	2.8×10^{-05}	8.3×10^{-05}	1.3×10^{-04}	6.5×10^{-05}	7.2×10^{-05}	8.9×10^{-07}	9.4×10^{-07}	2.9×10^{-06}	3.0×10^{-06}

<45																										
45 to <55	2.0×10^{-07}	7.8×10^{-07}	3.1×10^{-06}	3.6×10^{-06}	2.9×10^{-06}	3.3×10^{-06}	2.0×10^{-04}	2.8×10^{-04}	3.3×10^{-05}	4.8×10^{-05}	2.7×10^{-07}	3.6×10^{-07}	7.0×10^{-05}	7.4×10^{-05}	6.4×10^{-06}	6.8×10^{-06}	2.4×10^{-05}	2.8×10^{-05}	8.3×10^{-05}	1.3×10^{-04}	6.4×10^{-05}	7.1×10^{-05}	8.8×10^{-07}	9.3×10^{-07}	2.9×10^{-06}	3.0×10^{-06}
55 to <65	1.8×10^{-07}	7.2×10^{-07}	2.8×10^{-06}	3.4×10^{-06}	2.6×10^{-06}	3.1×10^{-06}	1.9×10^{-04}	2.5×10^{-04}	3.1×10^{-05}	4.4×10^{-05}	2.5×10^{-07}	3.4×10^{-07}	6.5×10^{-05}	6.8×10^{-05}	5.9×10^{-06}	6.3×10^{-06}	2.3×10^{-05}	2.6×10^{-05}	7.7×10^{-05}	1.2×10^{-04}	6.0×10^{-05}	6.6×10^{-05}	8.2×10^{-07}	8.6×10^{-07}	2.7×10^{-06}	2.8×10^{-06}
65 to <70	4.3×10^{-08}	1.7×10^{-07}	6.7×10^{-07}	8.0×10^{-07}	6.2×10^{-07}	7.2×10^{-07}	4.4×10^{-05}	6.0×10^{-05}	7.2×10^{-06}	1.0×10^{-05}	6.0×10^{-08}	7.9×10^{-08}	1.5×10^{-05}	1.6×10^{-05}	1.4×10^{-06}	1.5×10^{-06}	5.3×10^{-06}	6.1×10^{-06}	1.8×10^{-05}	2.8×10^{-05}	1.4×10^{-05}	1.6×10^{-05}	1.9×10^{-07}	2.0×10^{-07}	6.3×10^{-07}	6.6×10^{-07}
0 to <70	2.0×10^{-06}	8.0×10^{-06}	3.2×10^{-05}	3.8×10^{-05}	2.9×10^{-05}	3.4×10^{-05}	1.1×10^{-01}	1.5×10^{-01}	3.4×10^{-04}	4.9×10^{-04}	2.8×10^{-06}	3.7×10^{-06}	7.2×10^{-04}	7.6×10^{-04}	1.9×10^{-04}	2.1×10^{-04}	3.6×10^{-04}	4.1×10^{-04}	8.5×10^{-04}	1.3×10^{-03}	6.6×10^{-04}	7.3×10^{-04}	9.1×10^{-06}	9.6×10^{-06}	3.0×10^{-05}	3.1×10^{-05}

Table S2 - Estimated fractional hazard index by age and hazard index (HI) for a lifetime for exposure to essential and non-essential elements in rice by major effect

	Neurological		Gastrointestinal		Urinary		Hematological		Nervous	
Age	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile	Mean	95th percentile
< 1	1.0×10^{-05}	1.6×10^{-05}	9.0×10^{-06}	9.5×10^{-06}	2.5×10^{-03}	3.4×10^{-03}	1.2×10^{-05}	1.5×10^{-05}	1.2×10^{-05}	1.3×10^{-05}
1	5.8×10^{-05}	9.1×10^{-05}	5.1×10^{-05}	5.4×10^{-05}	1.4×10^{-02}	1.9×10^{-02}	7.0×10^{-05}	8.5×10^{-05}	6.6×10^{-05}	7.2×10^{-05}
2	4.6×10^{-05}	7.3×10^{-05}	4.1×10^{-05}	4.3×10^{-05}	1.1×10^{-02}	1.5×10^{-02}	5.6×10^{-05}	6.8×10^{-05}	5.3×10^{-05}	5.8×10^{-05}
3	4.5×10^{-05}	7.1×10^{-05}	4.0×10^{-05}	4.2×10^{-05}	1.1×10^{-02}	1.5×10^{-02}	5.5×10^{-05}	6.7×10^{-05}	5.2×10^{-05}	5.6×10^{-05}
4	4.4×10^{-05}	6.9×10^{-05}	3.9×10^{-05}	4.1×10^{-05}	1.1×10^{-02}	1.5×10^{-02}	5.3×10^{-05}	6.5×10^{-05}	5.0×10^{-05}	5.5×10^{-05}
5	3.5×10^{-05}	5.4×10^{-05}	3.1×10^{-05}	3.2×10^{-05}	8.5×10^{-03}	1.1×10^{-02}	4.2×10^{-05}	5.1×10^{-05}	3.9×10^{-05}	4.3×10^{-05}
6	3.2×10^{-05}	5.0×10^{-05}	2.8×10^{-05}	3.0×10^{-05}	7.8×10^{-03}	1.1×10^{-02}	3.9×10^{-05}	4.7×10^{-05}	3.6×10^{-05}	4.0×10^{-05}
7	2.8×10^{-05}	4.4×10^{-05}	2.5×10^{-05}	2.6×10^{-05}	6.9×10^{-03}	9.4×10^{-03}	3.4×10^{-05}	4.2×10^{-05}	3.2×10^{-05}	3.5×10^{-05}
8	2.6×10^{-05}	4.0×10^{-05}	2.3×10^{-05}	2.4×10^{-05}	6.3×10^{-03}	8.5×10^{-03}	3.1×10^{-05}	3.8×10^{-05}	2.9×10^{-05}	3.2×10^{-05}
9	2.2×10^{-05}	3.5×10^{-05}	2.0×10^{-05}	2.1×10^{-05}	5.5×10^{-03}	7.4×10^{-03}	2.7×10^{-05}	3.3×10^{-05}	2.5×10^{-05}	2.8×10^{-05}
10	1.7×10^{-05}	2.6×10^{-05}	1.5×10^{-05}	1.6×10^{-05}	4.1×10^{-03}	5.5×10^{-03}	2.0×10^{-05}	2.5×10^{-05}	1.9×10^{-05}	2.1×10^{-05}
11	1.5×10^{-05}	2.3×10^{-05}	1.3×10^{-05}	1.4×10^{-05}	3.6×10^{-03}	4.9×10^{-03}	1.8×10^{-05}	2.2×10^{-05}	1.7×10^{-05}	1.8×10^{-05}
12	1.3×10^{-05}	2.1×10^{-05}	1.2×10^{-05}	1.2×10^{-05}	3.2×10^{-03}	4.3×10^{-03}	1.6×10^{-05}	1.9×10^{-05}	1.5×10^{-05}	1.6×10^{-05}
13	1.2×10^{-05}	1.9×10^{-05}	1.0×10^{-05}	1.1×10^{-05}	2.9×10^{-03}	3.9×10^{-03}	1.4×10^{-05}	1.7×10^{-05}	1.3×10^{-05}	1.5×10^{-05}
14	1.1×10^{-05}	1.7×10^{-05}	9.7×10^{-06}	1.0×10^{-05}	2.7×10^{-03}	3.6×10^{-03}	1.3×10^{-05}	1.6×10^{-05}	1.3×10^{-05}	1.4×10^{-05}
15	1.0×10^{-05}	1.6×10^{-05}	9.1×10^{-06}	9.6×10^{-06}	2.5×10^{-03}	3.4×10^{-03}	1.2×10^{-05}	1.5×10^{-05}	1.2×10^{-05}	1.3×10^{-05}
16	9.9×10^{-06}	1.6×10^{-05}	8.8×10^{-06}	9.3×10^{-06}	2.4×10^{-03}	3.3×10^{-03}	1.2×10^{-05}	1.5×10^{-05}	1.1×10^{-05}	1.2×10^{-05}
17	9.6×10^{-06}	1.5×10^{-05}	8.5×10^{-06}	9.0×10^{-06}	2.3×10^{-03}	3.2×10^{-03}	1.2×10^{-05}	1.4×10^{-05}	1.1×10^{-05}	1.2×10^{-05}
18	9.3×10^{-06}	1.5×10^{-05}	8.2×10^{-06}	8.7×10^{-06}	2.3×10^{-03}	3.1×10^{-03}	1.1×10^{-05}	1.4×10^{-05}	1.1×10^{-05}	1.2×10^{-05}
19	9.4×10^{-06}	1.5×10^{-05}	8.3×10^{-06}	8.8×10^{-06}	2.3×10^{-05}	3.2×10^{-05}	1.1×10^{-05}	1.4×10^{-05}	8.1×10^{-06}	8.9×10^{-06}
20 to <25	4.5×10^{-05}	7.1×10^{-05}	4.0×10^{-05}	4.2×10^{-05}	1.1×10^{-04}	1.5×10^{-04}	5.5×10^{-05}	6.7×10^{-05}	3.9×10^{-05}	4.3×10^{-05}
25 to <30	4.3×10^{-05}	6.8×10^{-05}	3.8×10^{-05}	4.0×10^{-05}	1.1×10^{-04}	1.5×10^{-04}	5.2×10^{-05}	6.4×10^{-05}	3.7×10^{-05}	4.1×10^{-05}
30 to <35	4.2×10^{-05}	6.7×10^{-05}	3.8×10^{-05}	4.0×10^{-05}	1.1×10^{-04}	1.4×10^{-04}	5.1×10^{-05}	6.3×10^{-05}	3.6×10^{-05}	4.0×10^{-05}
35 to <45	8.4×10^{-05}	1.3×10^{-04}	7.4×10^{-05}	7.8×10^{-05}	2.1×10^{-04}	2.8×10^{-04}	1.0×10^{-04}	1.2×10^{-04}	7.1×10^{-05}	7.9×10^{-05}
45 to <55	8.3×10^{-05}	1.3×10^{-04}	7.3×10^{-05}	7.8×10^{-05}	2.1×10^{-04}	2.8×10^{-04}	1.0×10^{-04}	1.2×10^{-04}	7.1×10^{-05}	7.8×10^{-05}
55 to <65	7.7×10^{-05}	1.2×10^{-04}	6.8×10^{-05}	7.2×10^{-05}	1.9×10^{-04}	2.6×10^{-04}	9.3×10^{-05}	1.1×10^{-04}	6.6×10^{-05}	7.2×10^{-05}
65 to <70	1.8×10^{-05}	2.8×10^{-05}	1.6×10^{-05}	1.7×10^{-05}	4.5×10^{-05}	6.1×10^{-05}	2.2×10^{-05}	2.7×10^{-05}	1.5×10^{-05}	1.7×10^{-05}
0 to <70	8.5×10^{-04}	1.3×10^{-03}	7.6×10^{-04}	8.0×10^{-04}	1.1×10^{-01}	1.5×10^{-01}	1.0×10^{-03}	1.3×10^{-03}	8.6×10^{-04}	9.4×10^{-04}

6. CONSIDERAÇÕES FINAIS

Foi realizada uma avaliação de riscos à saúde humana devido ao consumo de arroz e cereais infantis feitos de arroz, uma vez que que este é um cereal amplamente consumido no Brasil, e que reconhecidamente armazena quantidades significativas de arsênio inorgânico, considerado carcinogênico e associado a outros efeitos não carcinogênicos à saúde (FDA, 2016; IBGE, 2020). Uma vez que a água de consumo pode ser também uma fonte de arsênio, esta foi incluída nesta avaliação de riscos. Quantificar os riscos de uma exposição é o primeiro passo para mitigá-los, e neste caso pode proporcionar melhorias para a saúde pública.

De acordo com os dados, cenário de exposição e método utilizados, o consumo combinado de arroz, água e cereais infantis resulta em um incremento de risco de câncer no tempo de vida considerado elevado, que varia de $7{,}4 \times 10^{-05}$ a $2{,}4 \times 10^{-04}$. O menor valor é referente ao consumo de arroz integral e cereais infantis de milho, e tal resultado deve ser interpretado como a probabilidade de que 7,4 em 100.000 pessoas desenvolvam câncer decorrente de tal exposição. O pior cenário refere-se ao consumo de arroz branco e cereais infantis feitos de arroz, representando 2,4 casos de câncer em 10.000 devido a esta exposição. Não existe um valor de referência de risco tolerável para consumo de alimentos. Alguns autores utilizam o valor descrito pela EPA para avaliar áreas contaminadas, que estabelece como aceitável o risco de câncer no intervalo de 10^{-4} a 10^{-6} (SHARMA et al., 2020; AL-SALEH et al, 2017; SHIBATA et al., 2016). Usando tal referência como parâmetro, é possível afirmar que o consumo de arroz branco, cereais infantis feitos de arroz e água no Brasil pode representar um risco 2,6 vezes maior que o tolerável.

O consumo de arroz isoladamente já representa um risco significativo devido a presença de arsênio inorgânico, sendo a média e percentil 95 respectivamente $1{,}4 \times 10^{-04}$ e $2{,}3 \times 10^{-04}$ para arroz branco, e $5{,}4 \times 10^{-06}$ e $7{,}7 \times 10^{-06}$ para arroz integral. O menor risco decorrente do consumo de arroz integral deve-se a menor concentração média de arsênio inorgânico em parte das amostras de arroz integral, o que é incomum. Dado que as amostras de arroz branco e integral são de procedências distintas, há diversos fatores que poderiam ter contribuído para a baixa concentração de arsênio inorgânico do arroz integral, e que não incidiram no arroz branco. Neste trabalho, foram exploradas hipóteses para a baixa concentração de arsênio em tais amostras de arroz, que envolvem as características ambientais da área de plantio, práticas agrícolas e cultivares de arroz que acumulam menos arsênio, e que merecem investigações pois foi evidenciado que é possível produzir arroz com baixa concentração de arsênio inorgânico, de modo que seu consumo representaria um risco mais próximo do que se pode entender como tolerável. Portanto, recomenda-se estudos para verificar se tais fazendas de onde vieram as amostras de fato produzem arroz com baixa concentração de arsênio, e estudos que busquem entender estas dinâmicas que afetam a concentração de arsênio em arroz no Brasil. Caso confirme-se que já é plausível produzir arroz com baixas concentrações de arsênio inorgânico, seria possível adotar tais estratégias para promover a segurança alimentar.

Nas amostras de arroz analisadas, o arsênio inorgânico foi o único elemento que representou risco carcinogênico significativo, de modo que o chumbo não representou risco expressivo. Foi observada a presença de outros elementos reconhecidos como carcinogênicos para humanos (cadmio, alumínio e níquel), entretanto ainda não há fator de carcinogenicidade descrito na literatura para estes metais, de modo que não é possível estimar o risco de câncer decorrente de tal exposição (IARC, 2020).

O consumo de arroz apresentou-se seguro em termos de risco não carcinogênico para arsênio inorgânico, e todos os elementos tóxicos e essenciais incluídos nesta avaliação de riscos.

Neste contexto de exposição a arsênio, o consumo de água, que em muitos locais do mundo é considerada uma importante fonte de exposição, representou uma menor contribuição para o risco carcinogênico, entretanto, este foi considerado em média 6,5 vezes acima do valor tolerável de 10^{-5} descrito pela OMS, e o percentil 95 foi 19,7 vezes superior a tal valor (WHO, 2017). Para um resultado com menos incertezas, seria necessária e especiação do arsênio presente em água, uma vez que os dados de monitoramento nacional apresentam apenas a concentração de arsênio total em água para consumo humano, de modo que os resultados desta avaliação de risco estão superestimados. Portanto, recomenda-se estudos com a especiação do arsênio em água para consumo. O risco não carcinogênico decorrente do consumo de água não se mostrou significativo.

Dentre a população estudada, as crianças são o grupo mais vulnerável, e a literatura mostrou um consumo precoce de arroz e cereais infantis, que muitas vezes são feitos de arroz, no Brasil (ALBUQUERQUE et al 2018; SOMBRA et al 2017). O risco carcinogênico estimado para o consumo de cereais infantis foi considerado elevado, com destaque para os cereais contendo arroz na composição (4×10^{-5}), devido a típica elevada concentração de arsênio inorgânico no grão. Cereais infantis tendo arroz como principal componente apresentaram risco cerca de 12 vezes maior que o risco para cereais infantis sem arroz em sua composição, e 2 vezes maior do que os que continham uma mistura de cereais incluindo arroz.

Todas as amostras de cereais infantis apresentaram risco não-carcinogênico não tolerável, com ao menos um elemento com valor de quociente de perigo acima do valor de referência, indicando que efeitos à saúde decorrentes de tal exposição são prováveis. Cereais infantis à base de arroz demonstraram risco não carcinogênico mais significativo, com um maior número de substâncias acima do valor de referência para risco. Além dos elementos tóxicos, foi estimado que alguns elementos essenciais presentes em cereal infantil, adicionados durante o processo de produção, representam risco não carcinogênico significativo.

Para resultados com menos incertezas, recomenda-se estudos sobre consumo de cereais infantis que registrem as quantidades diárias de cereais infantis ingeridas, uma vez que tal dado ainda não é disponível para a população brasileira. Complementarmente, os resultados desta avaliação de riscos como um todo podem estar subestimados, pois há outros alimentos que são fonte de arsênio, como certos produtos feitos à base de arroz que não foram incluídos por falta de dados. Além disso, o risco para certas populações, como pessoas celíacas, que geralmente consomem mais arroz que a população em geral, provavelmente é mais elevado (PEDRON et al, 2016).

O chumbo não representou risco (carcinogênico e não carcinogênico) significativo nas estimativas realizadas decorrentes do consumo de cereais infantis e arroz branco, entretanto, conforme descrito pela FAO, nenhuma dose de chumbo provindo da dieta deve ser considerada segura (JOINT FAO/WHO, 2011b). Portanto, a exposição a chumbo presente em arroz e cereais infantis envolve riscos à saúde.

Seguir o valor de referência (nacional e internacional) para arsênio inorgânico em arroz, demonstrou-se não ser protetivo à saúde de acordo com o cenário brasileiro, uma vez que neste trabalho foram levados em conta as características físicas populacionais e a frequência e quantidade de consumo de arroz pela população brasileira.

A avaliação de riscos, neste contexto, mostra-se como uma importante ferramenta para a estimativa e gestão dos riscos referente ao consumo de arroz, portanto tendo o potencial de gerar benefícios para a saúde pública. A estimativa dos riscos de acordo com o método adotado neste trabalho pode trazer resultados com menos incertezas, comparada a outras abordagens, o que é endossada pela FAO (2015).

Foi demonstrado neste trabalho que o risco devido ao consumo de arroz e cereais infantis poderia ser reduzido, o que entretanto demandaria ações que abarcassem a complexidade do cenário brasileiro. A redução do limite máximo de contaminante permitido em arroz no Brasil, acompanhado de ações voltadas às práticas agrícolas, industriais e culturais dos consumidores, poderiam ser um caminho para a redução do risco. Estudos e políticas públicas seriam essenciais para alcançar tais objetivos, especialmente no que se refere à redução de risco associado a idades precoces, onde adiciona-se ao cenário o incentivo a amamentação exclusiva até os 6 meses de idade. Alguns países têm obtido sucesso em gradualmente incentivar a indústria a produzir arroz com menor concentração de arsênio inorgânico para a população em geral, ou para populações específicas, como crianças. Nos estados Unidos da América, a FDA, a partir de avaliações de risco, implementou um programa para incentivar a indústria de cereais infantis a adotar reconhecidas boas práticas para produzir cereais com baixa concentração de arsênio, como diluir a concentração de arsênio inorgânico adicionando outros tipos de cereais à composição do produto, selecionar bons fornecedores, e realizar testes de concentração de arsênio inorgânico sempre que recebem arroz para produção (U.S.FDA, 2020).

Este trabalho se insere em um contexto complexo, e por isso teve apenas como objetivo entender o risco associado principalmente ao consumo de arroz de acordo com o método de avaliação de riscos, e estimar a redução do risco decorrente de possíveis medidas de mitigação. Novos trabalhos, de outras áreas e interdisciplinares, são fundamentais para que se investigue melhores maneiras de se mitigar o risco no contexto brasileiro. Além de investigações na área da agronomia, uma análise a respeito dos processos industriais, da gestão da cadeia de produção, e o entendimento a respeito dos impactos econômicos de cada possível medida de mitigação, identificando quais são as mais viáveis dentro do cenário nacional, seriam importantes. Tais estudos seriam essenciais para pautar políticas públicas voltadas para esta questão, garantindo que o arroz chegue ao consumidor representando baixo risco à saúde.

No Brasil, a ANVISA é o órgão responsável por determinar o limite máximo de arsênio em arroz, e tal regulamentação é direcionada para o Mercosul. Portando, alterar o limite máximo de arsênio inorgânico em arroz implicaria impactos no comércio exterior. Atualmente a ANVISA determina um limite máximo de 200 ng g^{-1} de arsênio total, de modo que teoricamente força o arroz comercializado no Brasil a ter menos arsênio inorgânico que os demais países, que seguem uma diretriz de limite máximo de 200 ng g^{-1} arsênio inorgânico. Entretanto, a ANVISA está em processo de padronização com os limites internacionais, o que vai permitir que o arroz no Brasil tenha maiores concentrações de arsênio inorgânico que o que temos até o momento (ANVISA, 2020).

No que tange o risco voltado para crianças, políticas públicas voltadas para a educação, incentivando a amamentação, retardando a introdução de alimentos e diversificando a alimentação infantil, com ações direcionadas a famílias e profissionais da saúde, poderiam ter um impacto importante na mitigação do risco. A proposição de medidas para lidar com uma realidade em que muitas mães não têm licença maternidade e por isso não conseguem amamentar seriam de grande relevância.

Seguindo os princípios da segurança alimentar, espera-se que as políticas públicas para mitigação dos riscos sejam principalmente direcionadas para agricultura e indústria, de modo que garanta que o arroz chegue aos consumidores com baixo teor de arsênio inorgânico, representando baixo risco à saúde.

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8. CURRÍCULOS LATTES

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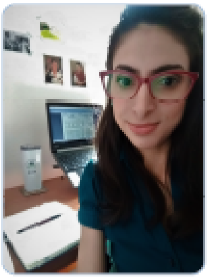

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2016 - 2016	Análise, Avaliação e Gerenciamento de Risco. (Carga horária: 40h). Companhia de Tecnologia de Saneamento Ambiental, CETESB, Brasil.
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